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Vol. XXII, No. 5 MAY, 1933

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

CONTENTS

Frontispiece and Sketch—Model and Progress of the American Pharmacy Building 375
Editorial:
- Madison Next 376
- Proposed Amendment or Revision of the National Food and Drugs Act 376
- "Academic and Industrial Research in the Field of Therapeutics" 379
- Confidence and Coöperation Essential to Progress 380

Scientific Section:
- The Effect of Aging upon the Potency of Digitalis Tinctures—Foster and Van Dyke 381
- Amino-Alcohols. IX. Biologic Assay of Propadrin and Ephedrine—Githens, M.D. 391
- A Study of Senecio Riddellii—Bukey and Cunningham 399
- A Comparative Study of Two Xanthine Diuretics—Bliss, Jr., and Morrison 404
- Manganese Preparations for the Treatment of Fungous Infections—Taylor 410
- A Method for the Quantitative Determination of Minute Amounts of Peroxides in Ether—Green and Schoetzow 412
- The Preparation and Optical Rotation of Pure Quinidine—Butler and Cretcher 414
- Night Blue as an Indicator for Use in Volumetric Titrations of Alkaloids with Silicotungstic Acid—Feinstein and North 415
- Gasometric Analysis of Sodium Nitrite in Coated Tablets, in the Presence of a Bicarbonate and Nitrate—Dick 419

Bibliography of Pharmaceutical Research—DuMez 421
The Pharmaceutical Journals of the United States—Meyer 424
Assay of Aromatic Spirit of Ammonia, U. S. P. X—Booth 429
Animal Pharmaceuticals of the Past and Present—Whitebread 431
Pioneers in American Pharmacy 437
The Department of the American Association of Colleges of Pharmacy:
- Teaching Laboratory Work in Pharmacy—MacKnight 442
- Michigan's Pharmaceutical Achievement—Stocking 444
- Modern Trends in Educational Methods—Lemon 447

Committee Reports:
- Report on the Pan-American Medical Congress—Bradley 453

Official Pharmacopœias and Formularies in Use in the Different Countries of America—Galbis 454
Pan-American Pharmacopœial Uniformity—Cook, Ph.M 456
Prescription Tolerances 457
National Conference on Pharmaceutical Research 458
Proceedings of the Local Branches 460
Editorial Notes 466
Personal and News Items 468
Obituary 469
Societies and Colleges 471
Legal and Legislative 475
Book Notices and Reviews 477
Recent Usage of the Term "Pyrethrin"—Shepard 479
Advertising—Cover Pages 2, 3 and 4 and pp. I–XXIV.

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THE 81st ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN MADISON, WISCONSIN, AUGUST 28 TO SEPTEMBER 2, 1933, HOTEL LORAINE, HEADQUARTERS, EMERSON STANLEY, 602 CENTRAL BUILDING, MADISON, LOCAL SECRETARY.

The 1933 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Madison.

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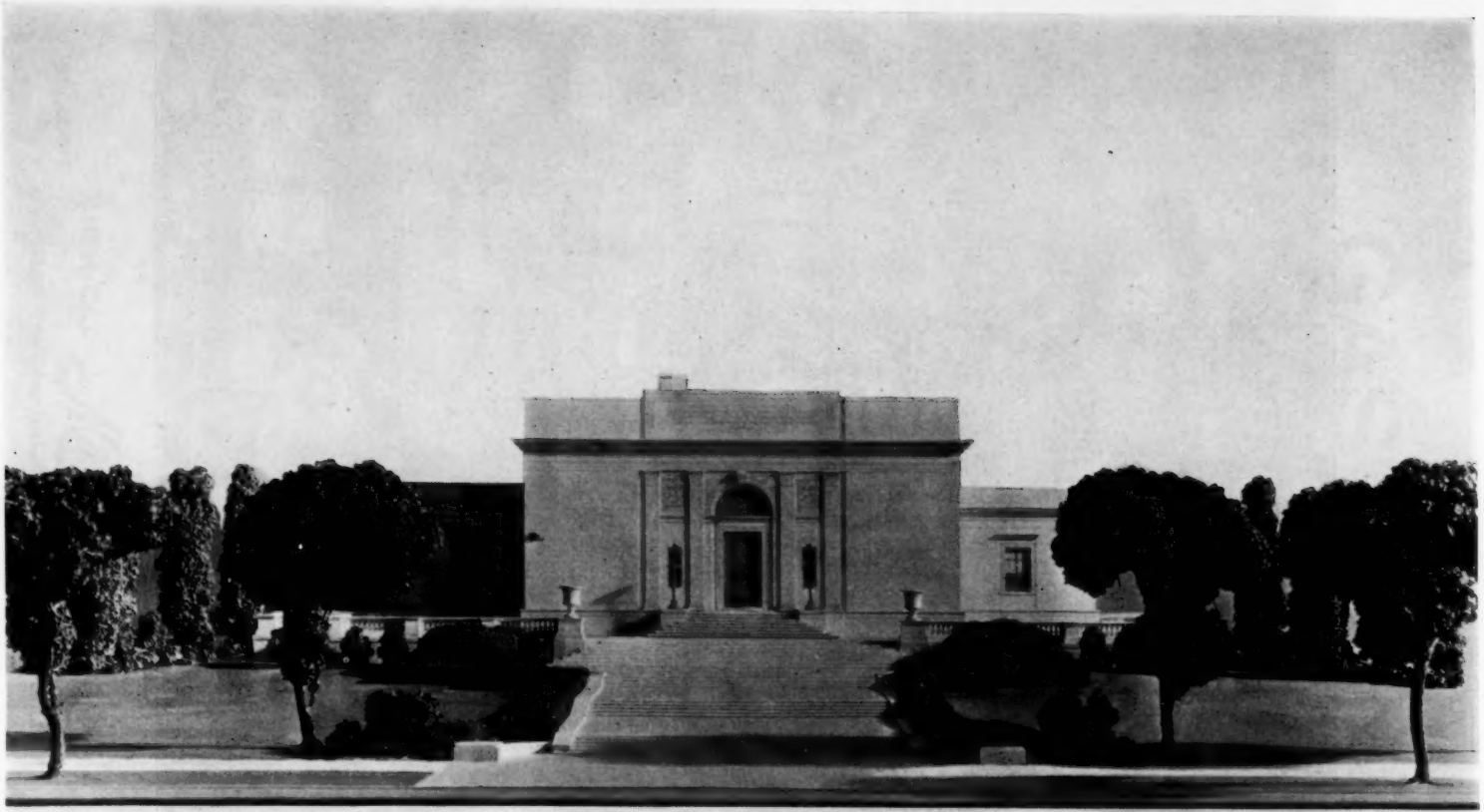

Model of the American Pharmacy Building, now in Science Hall, World's Fair, Chicago, modeled by Bertram L. Keyes; photo by Hughes Company.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXII MAY, 1933 No. 5

PROGRESS OF THE AMERICAN PHARMACY BUILDING.

THE picture on the page facing this was made from a photograph of a model of the building to be exhibited in Chicago at the World's Fair. The inscription reads:

"AMERICAN INSTITUTE OF PHARMACY."

"This Building is dedicated to those who have given of their thought and endeavor to the improvement of Public Health and to the further advancement of Science in Pharmacy."

The half-tone above, shows the status of the building at the time the photograph was taken about a month ago. The interior work is progressing rapidly; the landscaping is under way.

The model, as part of the Pharmacy Exhibit, will be seen by millions of visitors, estimated at 45,000,000. A brief editorial comment may be found in the April JOURNAL; see also page 1 and page 83, January and February issues, respectively.

...American Pharmacy Building, now in Science Hall, World's Fair, Chicago, modeled by Bertram L. Keyes; photo by Hughes Company.

EDITORIAL

E. G. EBERLE, EDITOR 10 West Chase Street, BALTIMORE, MD.

MADISON NEXT.

IT SEEMS only a little while ago since we met in Toronto, but it is not nearly as long to the time when the eighty-first session of the AMERICAN PHARMACEUTICAL ASSOCIATION will be convened in Madison, the beautiful University City surrounded by four Wisconsin lakes. The University buildings and campus are located on Lake Mendota. Longfellow's tribute reads:

"Four limpid lakes, four Naiades
Or Sylvan deities are these,
In flowing robes of azure dressed;
Four lovely handmaidens that uphold
Their shining mirrors rimmed with gold,
To the fair city of the west."

In the April number of the JOURNAL we introduced you to the Local Secretary; you should now become acquainted with the officers of the Sections; refer to the roster for them, beginning on page X. Partial programs should be printed in the next issue of the JOURNAL, papers can be mailed to the Section officers, later, and carbon copies may be mailed to the Editor, 10 West Chase St., Baltimore, Md. Abstracts of papers should be mailed to the respective secretaries, so that they may be manifolded for publicity in the pharmaceutical publications, and serve for the presentation of papers that cannot be submitted within time-limits. If the officers and contributors of papers will do their part the program can be published without undue haste.

It is hoped to have information relative to rates and routes and hotel charges in the June issue. Most of those going to Madison will, probably, arrange for a visit to the World's Fair, going or coming to the Madison meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION.

In this number, on a preceding page, is a picture of a photograph of a model of the Pharmacy Building exhibited at the World's Fair in Chicago and on another, page 375, is a print of the Pharmacy Building as it appeared about a month ago.

Each state and national association will desire to report on the progress being made toward the completion of the headquarters, and as endowments should be provided, associations and individuals have opportunities that will be welcomed.

One mounted photograph of the model of the Building has been mailed to each state pharmaceutical association.

PROPOSED AMENDMENT OR REVISION OF THE NATIONAL FOOD AND DRUGS ACT.

THE AMERICAN PHARMACEUTICAL ASSOCIATION came into being as the outcome of a meeting of representatives of the then existing four Colleges of Pharmacy called, in 1851, to consider the best means to prevent the importation of substandard and adulterated drugs. To prevent sophistication and to raise the standards of drugs has been one of its chief interests.[1] It promptly took an active part in the revision of the United States Pharmacopœia; later, it established the

National Formulary to meet a need for standards that the U. S. P. could not supply. The issuance of the Recipe Book and the work of the Committee on Unofficial Standards are extensions of the effort and many other contributions are cited in the "Standards Year Book" issued by the Bureau of Standards.

The ASSOCIATION has consistently supported legislation to regulate the quality of drugs and to legalize and enforce standards for their identity, purity and strength. It took an active interest in the Pure Food and Drug Congress, a voluntary organization to promote national legislation on the subject. Its members had an important part in drafting the national and state acts and, particularly, in having the U. S. P. and N. F. named in these acts as providing standards for drugs when furnished under official names.

In its report to the ASSOCIATION, in 1906, the Committee on National Legislation—Albert E. Ebert, chairman—observed that,

> "While this law in some directions goes far beyond the intent of its original promoters, it is, on the whole, a reasonable and conservative measure; and, if wisely and impartially administered, should benefit not only the general public, but the drug trade also. Every pharmacist should welcome a law designed to secure to the trade, drugs of standard strength and purity. It is true that nothing in this law prohibits traffic in goods of inferior quality, but the law does require such drugs to be labeled for what they are; and, when this law is fairly in operation, no pharmacist who has eyes to see and a determination to know, need have any fear of having inferior goods imposed upon him."

During the intervening twenty-six years, the law has been reasonably enforced and the results bear out the Committee's prediction. A tremendous advance has been made in the quality of foods and drugs and the American people have benefited beyond the expectations of those who worked for the legislation. The general opinion is that the Food and Drugs Act is one of the most effective and best enforced federal and state laws. The absence of demand for amendment, except in the field of advertising, is evidence.

No surprise should follow the recent announcement by Federal authorities that enforcement over a quarter of a century and developments with respect to foods and drugs during that time have developed defects in the law and also shown the need for additions. A number of changes are recognized as desirable by the pharmaceutical profession and industry, including the producers of proprietary medicines. The profession and industry were concerned, however, when it was proposed that the Act should be entirely rewritten on the ground that it was obsolete, and should include some provisions that appeared to be radical in effect and unjustified by experience.

A wealth of judicial opinion and of regulation has been accumulated which would be lost by a complete revision of the Act. Fundamentally the law is sound and to a large extent accomplished the purposes intended. All this should be conserved and the Act *amended* to take care of deficiencies and of additions made advisable by new conditions.

Conservative supporters of the Act cannot but be disturbed by the attitude of Government officials, which has not been frank, and by the rumored re-writing

[1] The Constitution of the AMERICAN PHARMACEUTICAL ASSOCIATION, Article I, Object 1, reads:

"To improve and regulate the drug market by preventing the importation of inferior, adulterated or deteriorated drugs and by detecting and exposing home adulterations."

of the Act by those who may be forward-looking but inexperienced. On the other hand, pharmaceutical interests must coöperate to conserve the present act and should not oppose reasonable changes, but should guide them so as to benefit the public and pharmacy. This was the sound policy of pharmacy in the drafting of the original act as well as of the narcotic and liquor laws.

Pharmacists are licensed by society to protect its interests in a necessary and dangerous service requiring specialized knowledge. They should not support over-zealous officials nor those who for selfish or misguided reasons may oppose necessary amendments to the law. They should be mindful only of the interests of the people which are frequently at variance with the views of both groups just referred to.

The conference between officials of the Food and Drug Administration and of representatives of the profession and industry in Washington, on April 27th, was not productive of the results it should have been. Pharmaceutical representatives were informed that at least a tentative draft or outline of the proposed amendments or revision would be discussed. When this was not submitted and they were met with the request for their comments and suggestions, without preparation, confusion resulted. If a tentative draft or outline had been submitted with frank explanations and then the pharmaceutical representatives given the opportunity to confer, frank expressions and suggestions would, no doubt, have been forthcoming from them. As it was, the relation of the U. S. P. and N. F. to the Act was the only subject properly discussed, outside of the proposed inclusion of cosmetics.

In principle, there can be no reasonable objection by pharmaceutical interests to the several proposals the Government officials are said to have in mind. They do not question the constitutionality of the Act so far as the U. S. P. and N. F. are concerned and express satisfaction with their revision and with the standards and tests set up by them for drugs officially recognized. They ask in general, that: (1) The Secretary of Agriculture be given authority to promulgate additional tests or assays to establish that the standards of the U. S. P. and N. F. have been observed in such cases as the so-called "Ginger-Jake," where the dangerous conditions could not have been foreseen by the committees of revision and where time does not permit sufficiently prompt action by the committees through ad interim revision. (2) Some addition to the variation clause which will give the user accurate and easily understood information on the label about the extent and character of the deviation from the official standards. (3) Some control over advertising, similar in character and extent to that now exercised over labels. (4) A requirement for the labeling of all drugs and medicines; a possible addition to the list of drugs now required to be named on the label; a partial formula disclosure and a possible time-limit on products that deteriorate rapidly. (5) A requirement for the licensing of classes of manufacturers, if and as long as conditions may require for adequate control of abuses.

Pharmaceutical interests may well question the language of the proposed amendments to accomplish these proposals and the regulations that may be made under the amendments. Requests were submitted by all groups that pharmaceutical representatives be given the opportunity to study and submit opinions upon the amendments or revision when drafted and before submitted to Congress.

It is important to all concerned that this request be granted and, particularly, to the public.

If it is granted, pharmaceutical interests should be constructive in their approval or objection to suggestions by the officials based on experience and should show a willingness to consider and support reasonable strengthening of the Food and Drugs Act.

If it is not granted, discussion and disagreement will almost certainly follow in the committees of Congress. When officials and professionals disagree, laymen have to act for the people. The result has usually been unsatisfactory to all parties. It is to be hoped, therefore, that the pharmaceutical interests will be given the opportunity to contribute of their technical knowledge and experience to the improvement of the act and that they will use the opportunity if offered, to the best effect possible.—E. F. KELLY.

"ACADEMIC AND INDUSTRIAL RESEARCH IN THE FIELD OF THERAPEUTICS."

SIR HENRY H. DALE, director of the National Institute for Medical Research, London, and secretary of the Royal Society of London, delivered the Dohme Lectures at Johns Hopkins and the address at the opening ceremony of the Merck Research Laboratories. The activities of this research worker are representative of the text of his addresses on the occasions referred to. He referred to Dr. Reid Hunt's investigations and his own at a somewhat later period, which exemplifies the relationship of the research in industrially supported laboratories, in academic laboratories and in institutes supported by public funds. He states regarding the investigations referred to that "Acetylcholine thus passed from the class of synthetic curiosities into that of natural substances, and a fuller study of its action showed a remarkable relation between its effects on different organs and those produced by parasympathetic nerves. This work, in an industrially supported laboratory, had brought us no nearer to practical therapeutics than Professor Reid Hunt's original discovery had done; but it arose from a chance observation, for which only the industrial connection could have provided the opportunity, and of which we were able to take advantage through our association with large-scale work."

In referring to the laboratories of pharmaceutical houses of this country Dr. Dale said: "It must surely be generally recognized that some of the great advances in medical knowledge, which has in recent years come from American Universities, have been made possible by the coöperation which only industrially supported research could give."

The instructive dedication address was comprehensive, dealing with every phase of research activities, and these brief quotations have been selected for stressing the title of this comment. The writer asks pardon for not making more extended selections and comment and concludes with the following quoted paragraph:

"I have suggested, as the primary concern of the laboratories supported by Industry, the development to a practical outcome of the fundamental discoveries

which the academic and endowed institutions may be expected, in the main, to furnish. But just as the academic worker ought not to be restrained from following freely the line of his enquiry, because it happens to lead to a practical application, the investigator in an industrially supported laboratory ought to have a large freedom, to follow a clue to new knowledge of a fundamental kind, if it presents itself in the course of his practical investigations. Indeed, I think it is probably of great advantage to an industrial laboratory that its staff should have always in hand a substantial body of investigation having no direct relation to any practical development. My own personal experience, if you will pardon a further reference to it, perhaps influences my views unduly. If the Head of a great pharmaceutical house, who gave me my first real opportunity as an independent investigator, had been inclined to judge me by my output of therapeutic novelties directly remunerative to his firm, I think he must have concluded that I was a very unprofitable investment. If he did so, he never let me suspect it; on the contrary, I received a steady encouragement to follow, with my colleagues, the natural lead of the problems which our initially practical investigations had presented. And I believe that such a policy is undoubtedly the right one. If necessity is the mother of invention, the spirit of free investigation is most certainly its father. The men who work here will need it, to preserve their active interest in what is happening in the larger world of science, and to maintain their contacts with men of like interests in the academic world."

CONFIDENCE AND COÖPERATION ESSENTIAL TO PROGRESS.

THE idea has prevailed too much in private, national and international affairs that relationship is based on economic warfare. As a result there is lack of foresight, errors of judgment, selfishness, disregard as to the situation of the other fellow—and, in some cases, dishonesty. Few have been free from bank experiences that are not conducive to a fellow-feeling and, if the measure was applied reversely, there might result a better understanding of the fact that honesty is a principle, and the observance of every ethical and economic principle is good policy. The same applies to a related extent in the industries and in the professions. Constructive thought and action are necessary in pharmacy as in other activities; discord develops weakness. As in other activities changes are developing and these can be guided by coöperative efforts, not only of the bodies which are closely related but with the coöperation of those having related purposes in their services for the people. Pharmacy is well organized, workers are engaged in endeavoring to improve existing conditions, but there is need of better coöperation, of a fuller understanding of the course to pursue, not by division but by proper linking. Readjustment is going on in all lines and pharmacy may not be the exception; it is destined to be carried on so long as sickness and disease exist and the members of few professions have been more alive to the duties incumbent upon them and mindful of the obligations assumed in its practice.

In proper shaping of affairs the thought must lead that success depends on unison in action as far as this is reasonably possible and confidence within the groups is essential, strengthened by a right understanding with related activities.

SCIENTIFIC SECTION

BOARD OF REVIEW ON PAPERS.—*Chairman*, L. W. Rowe; John C. Krantz, Jr.; F. J. Bacon.

THE EFFECT OF AGING UPON THE POTENCY OF DIGITALIS TINCTURES.*

BY R. H. K. FOSTER AND H. B. VAN DYKE.

There has been considerable disagreement among different workers as to the effect of aging upon the potency of digitalis tinctures. Wokes, in two papers (1, 2), discussed the assay of aged digitalis tinctures of which the potency as estimated by assay in the frog was considerably reduced; assay of the same tinctures in the cat, however, indicated that there was no loss of potency. Woke's work, therefore, suggests that the glucosides which kill the frog are different from those which kill the cat. It is clearly important also to determine which method of assay is more suitable for the clinic. The experiments reported in this paper were undertaken not only to confirm Woke's observations by different methods but also to attempt to ascertain why the deterioration of aged tinctures could be shown only by assay in the frog. It is hoped later to report the results of clinical assays of aged and fresh tinctures.

METHODS.

Assays.—Assay in the cat was performed by the common method of continuous intravenous infusion, at a constant rate of about 1 cc. per minute, till death occurred. The cats were not fed on the day of assay. Artificial respiration was routinely administered by means of a Starling pump used with the anesthetizing apparatus designed by one of us (3). The injection was stopped and the final burette reading was taken when the blood-pressure fell to zero. Most of the tinctures used were sufficiently concentrated (25 per cent) so that the fluid injected contained only two per cent of alcohol by volume.

The technique used for assay in the frog depended upon the intravenous injection, by the method of Smith and McClosky (4), of a diluted tincture (always containing 10 per cent of alcohol by volume), or of an aqueous extract of the residue of a tincture after removal of the alcohol in a vacuum desiccator at room temperature. Only male frogs were used. The brain was pithed and a suitably diluted extract was injected in a volume equivalent to 0.01 cc. per Gm. body weight; the same dose of the same preparation was ordinarily administered to 20 frogs. The hearts were examined in the usual way two hours after injection and the per cent mortality recorded.

Temperature control, which is important in any frog assay method, was effected by means of a specially constructed water-bath (Fig. 1).

The apparatus was made of rustless metal ("Allegheny"). The water of the large reservoir D, was maintained at 20° C. by means of a coil, through which cold water circulated, and a knife-blade heater controlled thermostatically. Water from D flowed through the outlet E into the individual frog compartments and thence through F, G, H and I_1. I_1 was connected with I_2 in Fig. 2 which illustrates the water pump operated by compressed air. When bottle R became filled, the rubber dam attached to cork float S closed the tubes O and T. Air from N raised the pressure in R and the water was forced up tube M and emptied into the main reservoir D of Fig. 1. When the bottle was emptied, the air escaped through the outlet tube M and as the pressure fell the valve S opened and the cycle was repeated. Tubes J, J, J and K served as outlet drains for emptying and cleaning the compartments. The 40 compartments were separated by partitions (A) and closed by hinged doors (B). X indicates small wire screen inserted in the

* From the Pharmacological Laboratory, University of Chicago.

overflows from each tier to prevent the frogs from closing the tube openings. The apparatus itself was enclosed in a larger asbestos board cabinet mounted on a galvanized steel framework with casters.

One hour before an experiment, the frogs were placed in the water-bath, usually a pair in each compartment. Before pithing, weighing and injecting, each was dried and the urine was expressed from its bladder. All injections were made into the musculocutaneous vein. If only two preparations were to be assayed, the standard and unknown solutions were injected alternately into pairs of similar frogs; each solution was given in the same dose per Gm. body weight to a group of 20 frogs.

The Accuracy of Assay in the Frog.—By the use of the intravenous technique described above a curve relating percentage mortality to *relative* dose was constructed by a method similar to that of Trevan (5). This was accomplished by twelve experiments each of which involved the use of two groups of twenty frogs. Inasmuch as all doses are computed as median lethal doses ("LD 50" (5)) Table I was calculated from the curve to facilitate the calculation of the LD 50, the median lethal dose having been given an arbitrary value of unity. If a standard and an unknown solution were to be compared in a given group of frogs, the median lethal dose of each was found by multiplying the dose administered by the factor appropriate for the mortality observed.

If a dose of digitalis producing a given mortality is to be considered significantly different from another dose producing the same mortality, providing that the probability of such a difference in random sampling is less than 0.01, the deviation in the median lethal dose is found graphically to be ± 14.4 per cent (-14.2 and $+14.6$ per cent); by calculation, in which K is estimated, the deviation of the median lethal dose is estimated at ± 15.3 per cent (see Trevan (5)). Therefore, if one assumes that the deviation of the median lethal dose is ± 14 per cent, the deviation in the ratio of potency of one preparation in terms of another will amount approximately to ± 28 per cent. In Table II are given the data of a group of experiments in which the LD 50 and ratio of potency were calculated for each pair of experiments in which the same dose of digitalis was administered to two similar groups of frogs. From the data on the possible ratios of potency (theoretical = 1.00), the standard deviation of the ratio of potency has been calculated as ± 0.086. For $p = 0.01$, the deviation must be increased to ± 0.289. It might, therefore, be concluded that a ratio of potency should be altered by more than ± 0.29 if such an alteration is to be regarded as clearly significant. However, if one computes the deviation of the ratio of potency from the experiments in which the observed mortalities fell on the "straight line" portion of the curve (excluding Experiments 1 and 8) the standard deviation of the ratio becomes ± 0.060 or, for $p = 0.01$, $3.7 \times 0.060 = \pm 0.222$.

The Effect of Alcohol upon Assay in the Frog.—In most of the experiments the solutions injected into the frog contained 10 per cent alcohol by volume. The effects of alcohol alone were first studied by injecting into seven groups of frogs 0.01 cc. of 20 per cent alcohol at assay-temperatures of 20° C. and 30° C. At the lower temperature no effect was observed in frogs recently obtained; however, two of 19 frogs, stored for several weeks, were killed by such a dose of alcohol. At 30° C. about 50 per cent of frogs stored for several weeks were killed by the alcohol

solution; from 14 to 35 per cent of fresh frogs were killed. It therefore appears that the effect of alcohol, especially at higher assay-temperatures, must not be disregarded.

TABLE I.—FACTORS FOR THE CONVERSION OF DOSES INTO THOSE KILLING FIFTY PER CENT OF A GROUP OF FROGS.

Observed Mortality.	0.	1.	2.	3.	4.	5.	6.	7.	8.	9.
0						1.47	1.44	1.41	1.39	1.37
10	1.34	1.32	1.30	1.29	1.27	1.25	1.24	1.23	1.22	1.21
20	1.20	1.19	1.18	1.17	1.16	1.15	1.14	1.13	1.13	1.12
30	1.11	1.10	1.10	1.09	1.08	1.08	1.07	1.07	1.06	1.05
40	1.05	1.04	1.04	1.03	1.03	1.02	1.02	1.01	1.01	1.00
50	1.00	1.00	0.99	0.99	0.98	0.98	0.97	0.97	0.97	0.96
60	0.96	0.95	0.95	0.94	0.94	0.93	0.93	0.92	0.92	0.91
70	0.91	0.90	0.90	0.89	0.89	0.88	0.88	0.87	0.87	0.86
80	0.85	0.85	0.84	0.83	0.83	0.82	0.81	0.81	0.80	0.79
90	0.78	0.77	0.76	0.75	0.74	0.74				

TABLE II.—CONTROL ASSAYS IN THE FROG.

Experiment No.	Tr. Digit.	Dose, Mg./Kg.	No. of Frogs.	Observed Mortality. Per Cent.	Calculated LD 50, Mg./Kg.	Possible Ratios of Potency.
1	A 13	208	20	15	260	1.16
		208	20	35	225	0.86
2	A 13	208	21	43	214	1.03
		208	20	50	208	0.97
3	A 13	208	20	40	218	1.05
		208	20	50	208	0.95
4	B 11	169	21	33	184	1.05
		169	22	41	176	0.95
5	C 5	159	20	25	183	1.13
		159	20	45	162	0.89
6	C 5	170	21	48	172	1.03
		170	20	55	167	0.97
7	C 5	191	20	70	174	1.00
		191	20	70	174	1.00
8	C 5	192	20	65	179	1.13
		192	20	85	157	0.88
9	C 12	189	20	60	181	0.98
		189	20	55	185	1.02

In a second set of experiments (Table III), the same dose of the same preparation with and without alcohol was administered to similar groups of frogs. The alcohol was removed from the digitalis tincture by the evaporation at room temperature of a measured volume in an agate mortar over P_2O_5 in a vacuum desiccator. The residue was triturated with saline solution and quantitatively transferred to a pyrex centrifuge tube, placed in a bath of boiling water for 5 minutes, cooled, made up to known weight and centrifuged. The results in Table III indicate, without exception, that a greater dose of glucoside(s) must be used in the absence of alcohol. Ten per cent of alcohol by volume appears to be equivalent, roughly, to an increase of 17 per cent in the dose of glucoside(s) (excluding the experiments with digitoxin).

Finally it may be asked whether or not the estimation of the ratio of potency of two preparations is affected by the presence of alcohol. Data in answer to this

question may be found in Table IV. Aged and fresh digitalis tinctures were compared in these experiments. The ratios of potency do not differ from each other significantly. The conclusion that a concentration of 10 per cent alcohol by volume does not seriously affect the estimation of the potency-ratio is justified, we believe, if the assay is carried out at 20° C.

TABLE III.—THE EFFECT OF ALCOHOL UPON ASSAYS IN THE FROG.

Experiment No.	Drug Used.	Alcohol Concentration by Volume, Per Cent.	No. of Frogs.	Observed Mortality, Per Cent.	Calculated LD 50, Mg./Kg.	Ratio of Dose without Alcohol to Dose with Alcohol.
212	Digitoxin	5.2	20	10	1.35	1.21
	"	15.2	20	30	1.12	
215	"	5	20	30	1.33	1.11
	"	15	21	48	1.20	
180	Ouabain	0	20	55	0.203	1.15
	"	10	21	81	0.176	
183	"	0	20	50	0.207	1.14
	"	10	21	76	0.182	
208	"	0	20	60	0.203	1.23
	"	10	20	90	0.165	
211	"	0	20	15	0.231	1.30
	"	10	20	60	0.177	
287	"	0	20	80	0.179	1.08
	"	10	21	62	0.165	
282	Tr. Digitalis A-15	0	20	75	227.0	1.15
	" " "	10	20	70	197.0	
286	" " "	0	20	55	253.0	1.17
	" " "	10	20	45	217.0	

TABLE IV.—THE LACK OF EFFECT OF ALCOHOL UPON THE RATIO OF POTENCY OF TINCTURES OF DIGITALIS AS DETERMINED BY ASSAY IN THE FROG.

Experiment No.	A Potency-Ratio (Alcohol, 10 Per Cent by Volume).	B Potency-Ratio (No Alcohol).	$\frac{A}{B}$.
238, 240	1.35	1.22	1.11
254, 244	1.29	1.23	1.05
250, 252	1.40	1.40	1.00
262, 276	1.44	1.53	0.94

METHODS OF EXTRACTION.

The method of Joachimoglu (6), slightly modified, was employed to insure the complete extraction of the different powdered digitalis samples. By the use of absolute alcohol in a Landsiedl extraction-apparatus, the leaves were continuously extracted for eight hours by alcohol near its boiling point. This time was chosen as a result of some control experiments which are shown graphically in Fig. 3. However, the potency of the extracts after only four hours' extraction is not significantly less than that after eight hours' extraction.

The adequacy of the method of extraction has also been studied by the assay of a number of fresh extracts of three different lots of digitalis leaves. Twenty-five such assays have been done in the cat, the average number of cats used for each assay being about seven. Only in three assays did the question of a significant difference in potency arise. In these three cases the probabilities that one would

obtain as great differences in random sampling were 0.017, 0.015 and 0.017 (calculated by the method of Fisher (7)). We have therefore, in subsequent assays, assumed that a significant change in potency as estimated by assay in the cat, has not occurred unless the probability of the occurrence of such a value, in random sampling is less than 0.01.

Nine pairs of different extractions were assayed in the frog by the method used in Table II. The only difference lay in the use of different extracts of the same leaf in the same dose for the comparison instead of the same extract in the same dose. On the assumption that in this set of experiments the theoretical ratio of potency is 1.000, the standard deviation is found to be ± 0.087. The results (including four experiments in which one or both mortalities lay outside the "straight line" portion of the curve relating relative dose and mortality) are there-

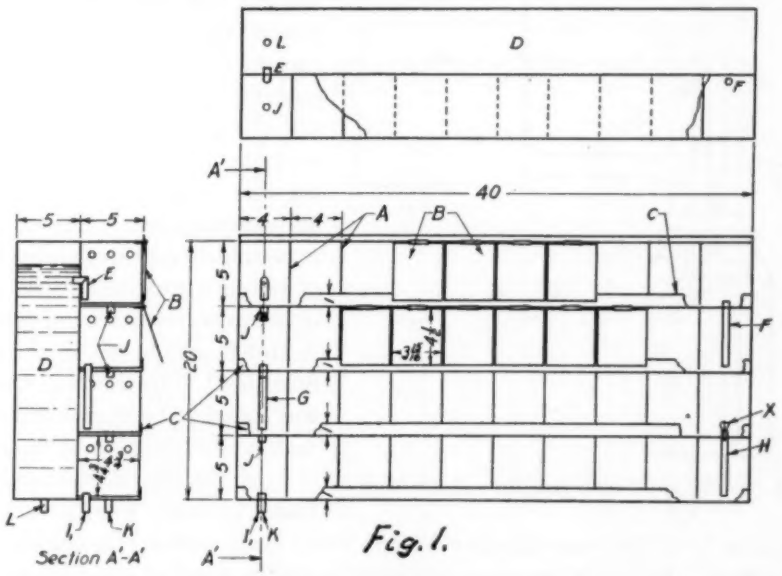

Fig. 1.—Constant temperature apparatus for assay in the frog. (Dimensions are given in inches.)

fore the same as those of the experiment in which pairs of extracts known to be identical were compared. Assay of different extracts in the frog, therefore, demonstrates that the extraction-procedure yields comparable extracts of uniform potency.

Extracts were also made by means of cold absolute alcohol. For this purpose extraction was carried out in a glass tube one and one-half by thirty-six inches; by the removal of small amounts of alcohol each day, the extraction was continued for two to three weeks. We are aware that extraction at room temperature can be performed adequately only with more dilute alcohol; however, it seemed best for purposes of comparison to employ absolute alcohol.

DIGITALIS SAMPLES.

Three different samples of digitalis leaves were employed: "A," Canadian, 1927, "B," Canadian, 1928 and "C," Minnesota, 1928.[1] Each sample was thor-

[1] Kindly donated by Mr. F. A. Upsher Smith.

oughly mixed and stored in brown glass bottles at room temperature. Dried to constant weight at 105° C., A was found to contain 7.74 per cent water, B and C, 8.30 and 7.36 per cent, respectively. The data on the relative potency of the three samples are given in Table V. The mean lethal doses for the cat were obtained by the use of 50 cats each for Samples A and B, and 60 cats for Sample C. One experiment each was performed in comparing potency in the frog by direct comparison (the three samples being assayed simultaneously) and by comparison in pairs. Finally two sets of determinations were carried out in the frog by the use of ouabain as a standard. In the first set of experiments, comparisons with ouabain were made twice with each sample; similar frogs were used for all comparisons. The second set of experiments represents the mean ratios of potency observed at different times in six experiments each with Samples A and B and seven experiments with Sample C. In the frog, one Gm. of A was found to be equivalent to approximately 0.95 mg. of U. S. P. ouabain.[1]

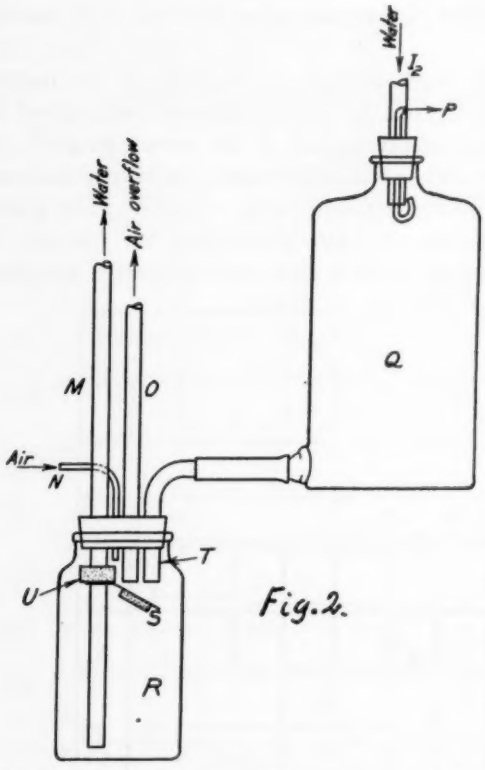

Fig. 2.

Fig. 2.—Water pump operated by compressed air.

In all the determinations, A is found to be the least potent. B and C appear to be of the same potency except when their potency is compared directly in the frog. However, more experiments should be done to establish this apparent difference.

TABLE V.—A COMPARISON OF THE POTENCY OF THE THREE DIGITALIS SAMPLES.

Digitalis Leaf.	Cat Assay. Mean LD. mg./Kg.	Cat Assay. Relative potency.	Frog Assay. Relative Potency as Determined by Direct comparison.	Comparison in pairs.	Use of ouabain (1) as standard.	(2)
A	76.8	90	76	73	86	82
B	68.5	99	89	88	97	99
C	68.9	100	100	100	100	100

THE LOSS OF POTENCY THROUGH AGING.

If tinctures of digitalis are permitted to age in glass-stoppered, paraffin-sealed bottles in the cupboard at room temperature, the potency as tested in the frog unquestionably falls. The potency as tested in the cat falls less and not so convincingly (Table VI). Assays in both the cat and frog were done at intervals of 5 to 29 weeks; an effort was made to perform both assays in the same week although

[1] Kindly supplied by Dr. W. T. McClosky of the Bureau of Food and Drug Administration, Department of Agriculture.

this was not always possible. The values given for potency in the cat are based on a comparison with the assay performed when the tincture was first made. In the cases of three of the tinctures (A9, C1 and C4) the potency was significantly reduced

TABLE VI.—THE LOSS OF POTENCY OF AGING TINCTURES OF DIGITALIS.

	Assay in Cat.				Assay in Frog.			
Sample.	Age of Tr. weeks.	Number of cats.	A potency.	Standard error of mean, per cent of mean LD.	Age of Tr. weeks.	B potency.	Approx. Age of Tr. Weeks.	B / A
A-6	7	5	1.00	10.9	23	0.82	24	0.93
	24	5	0.88	7.8	29	0.80		
	36	10	0.93	3.8	37	0.92	37	0.99
	53	10	0.95	7.0	38	0.82		
	73	10	0.88	5.3	48	0.67[1]	51	0.71
					73	0.58[1]	73	0.66
A-8	4	10	1.00	5.5				
	30	10	0.93	3.4	30	0.68[1]	30	0.73
	53	10	0.86	4.4	52	0.67[1]	52	0.78
A-9	0	5	1.00	7.7				
	17	10	0.98	4.0	19	0.81	18	0.83
	34	10	0.74[1]	2.7	35	0.82	35	1.11
B-1	0	5	1.00	3.4	14	0.93		
	16	5	0.89	7.1	19	0.84		
	29	9	0.95	3.9	29	0.77[2]	29	0.81
	45	10	0.91	5.3	42	0.74[2]	44	0.81
	65	10	0.91	2.7	65	0.62[1]	65	0.68
B-4	3	8	1.00	4.0				
	32	10	0.92	6.4	32	0.78[2]	32	0.85
	52	10	0.93	4.3	52	0.67[1]	52	0.72
B-9	0	5	1.00	6.2				
	18	10	0.94	3.9	19	0.86	19	0.91
	38	9	0.90	2.5	36	0.86	37	0.96
C-1	1	5	1.00	4.4	14	0.81	15	1.01
	8	4	0.85	4.9	25	0.76[2]		
	16	5	0.80	5.4	30	0.77[2]	30	0.93
	29	10	0.83	5.2	44	0.72[1]		
	46	10	0.79[1]	2.7	45	0.69[1]	46	0.87
	65	11	0.64[1]	5.8	65	0.60[1]	65	0.94
C-4	1	4	1.00	6.0				
	29	10	0.87	4.1	30	0.73[2]	30	0.84
	51	10	0.77[1]	4.3	51	0.68[1]	51	0.88
C-5	0	5	1.00	6.8				
	16	10	0.93	4.6	19	0.80	18	0.86
	37	9	0.82	6.2	41	0.76[2]	39	0.93
Digitoxin	0	7	1.00	4.4	0	1.00* (1.00**)		
	11	4	0.50[1]	2.8	5	0.88 (0.79)		
					20	0.49[1] (0.59)		
	41	9	0.49[1]	5.8	41	0.46[1] (0.60)	41	0.94* (1.22**)
	58	10	0.53[1]	6.4	59	0.52[1] (0.73)	59	0.98 (1.38)

[1] Potency significantly reduced ($p = < 0.01$).

[2] Potency perhaps significantly reduced.

* In terms of absolute doses.

** In terms of ouabain.

(in the case of A9 after only 34 weeks' aging). Although without exception all other tinctures appear weaker, in no single case is this convincingly shown.

To estimate potency in the frog, each aged solution was compared with one freshly made. The potency was significantly reduced in six of the nine tinctures and probably was reduced in a seventh (C5). In Tinctures A9 and B9, aged 35 and 36 weeks, respectively, the potency was not significantly lower. That the frog assays indicate a greater degree of deterioration than do those in the cat is shown by the ratios given in the last column of Table VI.

A limited amount of a single sample of Merck's digitoxin was the only purified digitalis principle available to us for aging experiments. The initial mean lethal dose of this preparation for the cat was 0.344 mg. per Kg. (7 cats, S. E. of mean = ±0.015 mg.); the LD 50 for the frog was about 0.73 mg. per Kg. or one-fourth the potency of U. S. P. ouabain. As is shown in Table VI, this sample of digitoxin dissolved in absolute alcohol rapidly deteriorated so that after 20 weeks it had lost half of its potency; during the succeeding 39 weeks there was probably no additional deterioration. Inasmuch as the same reduction in potency was observed by assays in both the cat and the frog, the experiments with the digitoxin sample do not aid in interpreting the other data of Table VI.

THE EFFECT OF TEMPERATURE UPON ASSAY IN THE FROG.

Assays in the frog were undertaken at 30° C. not only to determine the alteration in absolute LD 50 but also to learn whether or not the potency of aged solutions was found to be as low as when assays were done at 20° C. A characteristic curve determined for 30° C. was not available; the "LD 50 doses" were calculated from the curve as determined at 20° C. The experiments could not be performed at the two temperatures simultaneously; it is believed, however, that by the use of similar frogs, the change in absolute dose has been determined fairly accurately. The "LD 50 dose" at 30° C. is 43 per cent (about half) of the LD 50 dose at 20° C. This statement is based upon 14 determinations at 30° C. and 15 determinations at 20° C. Similar results were obtained with both alcohol-free ouabain solutions and digitalis tinctures.

Assays carried out at 30° C. with aged and fresh tinctures were in no case significantly different from those done at 20° C. In general, however, the apparent loss of potency appeared to be less at the higher temperature (six comparisons at 20° C. and eight comparisons at 30° C.). Before any further conclusion can be drawn, however, more experiments must be performed.

EXPERIMENTS WITH TINCTURES MADE BY EXTRACTION AT ROOM TEMPERATURE.

Extraction of the digitalis samples was carried out with absolute alcohol at room temperature by the method described in the first part of this paper. Although such extraction may be carried out slowly over several weeks, the glucosides are still incompletely removed. A portion of each of these extracts was heated, by immersing in a bath of boiling water, in a reflux condenser for eight hours and then compared with a corresponding unheated portion to determine whether or not there was a significant change in the potency in the frog compared with that in the cat. The results are shown in Table VII and suggest that such heating reduces the potency as estimated in the frog. In individual experiments none of the differences are

TABLE VII.—A COMPARISON OF THE POTENCY OF FRESH HEATED AND UNHEATED TINCTURES MADE BY EXTRACTION WITH COLD ABSOLUTE ALCOHOL.

Sample.	Number of cats.	Assay in Cat. Mean LD and standard error of mean, Mg./Kg.	U/H potency.	Assay in Frog. LD 50, mg./Kg.	U/H potency.
AP-1H	5	180.3 ± 6.6	1.08	375	0.86
AP-1U	5	194.6 ± 9.4		322	
AP-5H	5	180.8 ± 14.6	0.99	437	0.88
AP-5U	5	178.7 ± 10.6		385	
BP-1H	5	178.9 ± 11.4	0.91	341	0.91
BP-1U	5	162.5 ± 9.0		309	
BP-2H	5	150.1 ± 6.8	0.84	394	0.76
BP-2U	5	126.2 ± 4.8		301	
CP-1H	7	143.2 ± 4.9	1.02	245	0.90
CP-1U	5	146.2 ± 12.1		220	
CP-2H	5	140.4 ± 10.2	0.86	300	0.84
CP-2U	5	120.1 ± 5.9		252	

H indicates a heated extract.
U indicates an unheated extract.

significant. On the other hand, the mean potency (six experiments) of the heated sample is 95 per cent of the unheated sample by assay in the cat, and 86 per cent of the unheated sample by assay in the frog.

Samples BP-1H and BP-1U were permitted to age for 39 weeks; two comparison assays were then made in the frog. The absolute doses were increased in both from about 325 mg. per Kg. to about 500 mg. per Kg. However, the heated sample was then found to be the stronger (109 and 105 per cent)—an observation suggesting that the unheated sample underwent more rapid deterioration.

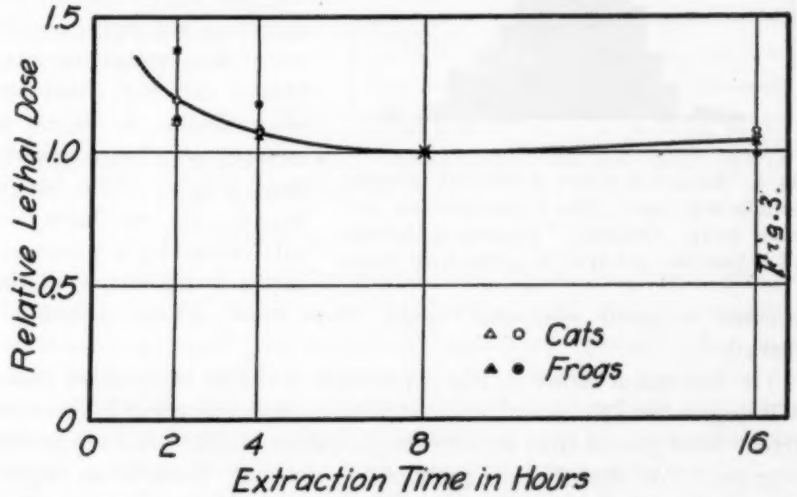

Fig. 3.—Efficiency of continuous extraction by hot absolute alcohol as determined by assay in the cat and in the frog.

DISCUSSION.

Our results confirm Woke's finding that tinctures of digitalis, if assayed in the frog, rather rapidly become weaker. On the other hand we found that although the

loss of potency as determined in the cat is usually much less, it may be nearly as great. Clinical assays of tinctures, which appear weaker only in the frog, are being undertaken in order to ascertain which method of assay is more accurate for the clinic. In so far as a conclusion may be drawn from one set of observations, it appears that a digitoxin solution, in aging a few months, loses about half of its potency as estimated in both the frog and the cat and therefore does not resemble an ordinary tincture of digitalis. Our data from experiments with tinctures made by extraction at room temperature suggest that at least part of the toxic action in the frog, rather than in the cat, is due to heat-labile substances.

We have not been able to correlate the degree of deterioration of a tincture (assay in cat or frog) with increased or increasing "p_H." On the contrary, Tinctures B1, B4 and B9 (Table VI), the potency of which in the cat was least affected by aging, were found to yield the highest glass-electrode potentials (+0.1937, 0.1909 and 0.1919 v. in comparison with 0.1858, 0.1811 and 0.1798 v. for the A group and 0.1752, 0.1709 and 0.1714 v. for the C group; 0.1 *N* HCl = −0.0494 v.). The estimates of the p_H of fresh two per cent aqueous extracts (infusions) were 5.78, 5.83 and 5.90 for Samples A, B and C.

The large number of assays performed enabled us to gather additional data bearing upon a few of the general questions relating to assay. In all seasons of the year, for example, U. S. P. ouabain was assayed in frogs. Our data consistently show that the frog (*R. pipiens*) is least susceptible in August (about 0.22 mg. per Kg.) and most susceptible in January (about 0.18 mg. per Kg.). Others (8) consider that frogs are more sensitive in summer. We observed no seasonal variation in cats nor could we correlate susceptibility in the cat more satisfactorily with heart weight than with body weight. Like McFarlane and Masson (9) we have noticed that cats exhibiting a pronounced bradycardia in the course of the injection commonly required somewhat larger doses than others receiving the same preparation.

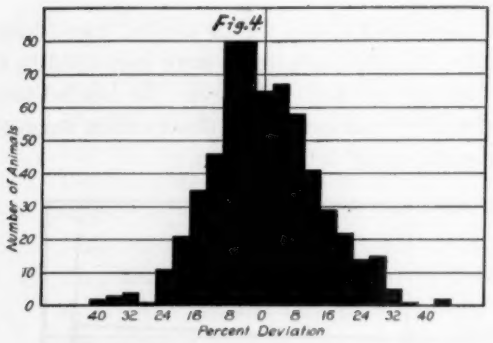

Fig. 4.—Results of assays of different tinctures of digitalis in 601 cats. Five to ten cats were used in each assay. Ordinate: number of animals killed. Abscissa: per cent deviation from mean.

The histogram shown in Fig. 4 probably is not as accurate as that of de Lind van Wijngaarden (10) inasmuch as it is based upon assays of different solutions in different sized groups (five to ten cats). Assays in 601 cats are represented in the histogram. The distribution probably is normal; there is no highly resistant group, such as McFarlane and Masson believe that they encountered.

SUMMARY.

1. The effect of aging upon the potency of digitalis tinctures was determined in the cat and frog (*R. pipiens*). In all cases the tinctures were made by extraction with absolute alcohol, usually with hot alcohol in a Landsiedl extractor. Assay in

the frog was performed by an intravenous technique. Various types of control experiments are described.

2. Aged tinctures were always found to be less potent by assay in both species; however, the greater reduction in potency was usually observed in the frog.

3. Deterioration of tinctures could not be correlated with increased "p_H;" on the contrary the tinctures most stable by cat-assay were shown to yield the highest glass-electrode potentials.

4. A sample of digitoxin in absolute alcohol lost about half of its toxicity toward both the frog and the cat after a few months. There was no further deterioration during the period of observation (59 weeks).

5. Frogs were found to be least susceptible to ouabain in the late summer (August).

6. The results of assays in 601 cats indicated that the distribution of susceptibility is probably normal.

We wish to thank Mr. F. A. Upsher Smith whose generous support made this investigation possible.

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AMINO-ALCOHOLS. IX. BIOLOGIC ASSAY OF PROPADRIN AND EPHEDRINE.*[1]

BY THOMAS S. GITHENS, M.D.

The physiologic assay of phenylpropanolamine (propadrin) and phenylpropanolmethylamine (ephedrine) is a problem which still awaits completely satisfactory solution. Although the qualitative action of ephedrine has been elucidated fairly thoroughly, and it is known to act on most, if not all, of the structures innervated by the autonomic system, none of these actions lend themselves to accurate quantitative analysis. Its actions on each of these structures differ so widely, quantitatively at least, from one animal to another and all are so markedly influenced by slight experimental differences which are not readily analyzed, that it is not possible to obtain quantitative determinations by comparing the action on one animal directly with that on another.

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* Presented under title "Bioassay of Propadrin Solutions," by T. S. Githens, James C. Munch and W. H. Hartung, before Scientific Section, A. PH. A., Toronto meeting, 1932.

[1] From The Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pa.

The effects which would seem to be most readily measured are those on the pupil, on isolated organs, such as the uterus and intestines, the dilation of the bronchi, which can be shown on the lung *in situ*, or isolated, and the pressor action, which is due to stimulation of the heart, associated with vaso-constriction. (Chen and Schmidt, *J. Am. Med. Assoc.*, 87 (1926), 836.) Studies by many authors of the effects on isolated organs and bronchi, have not shown such regularity as would recommend them for quantitative assays.

Swanson (*J. Pharmacol. & Exper. Therap.*, 38 (1930), 327) reports his findings on bronchodilatation from perfusion of the isolated lungs of 10 rabbits, 12 cats and 15 dogs. He used Sollmann and Van Oettingen's method, counting the bubbles per minute escaping in a Mariotte bottle. He does not report his results in detail, but gives a table showing the average increase of flow from 24 mg. added to the perfusion fluid, as 5 drops per minute. His published tracings show increases of flow varying from 3 to 9 drops per minute from a dose of 20 mg. This 300 per cent variation, which was even greater in our own work, illustrates the difficulty of obtaining quantitative results by this method.

Most biologically assayed drugs acting on the autonomic system, such as epinephrine and pituitary extract, are assayed by comparing the results obtained on a particular animal, or piece of tissue, with the effect produced on the same test object by a standard solution of the material being tested. In the case of ephedrine, however, this method is rendered illusory by the fact that its effect is reduced or altered by previous administration, so that whichever sample is first employed will appear to be the stronger. This reduced effect on repeated administration (tachyphylaxis) is true not only of its pressor action, on which it has been most carefully studied, but also of its effects on isolated tissues.

If a dog or cat be given by vein a dose of ephedrine which will cause a marked rise of pressure (*e. g.*, 0.5 to 2 mg. per kilo), and the same dose be repeated, even at intervals of several hours, the second dose will cause less rise than the first, the third still less, and eventually a fall may result. This lessened pressor effect probably depends mainly on the cardiac action of the drug, and is believed by Mügge (*Arch. exptl. Path. Pharmakol.*, 165 (1932), 230) to result from the fact that the flow through the coronary vessels is increased by the first injection and lessened by later doses. There is, however, no fixed relation between the rise caused by the first and by subsequent doses. This fact makes it impossible to "standardize" the test animal by giving a definite dose of a standard preparation and to base the assay on the relation between the rise caused by this and the rise following administration of a solution of unknown strength. If the doses are much smaller than that which gives a maximum response, this tachyphylaxis tends to become less with repetition of the dose, and eventually subsequent doses may give substantially identical effects, although the response is never as regular as it is with repeated injections of the same dose of epinephrine. Thus, Tainter (*J. Pharmacol. & Exper. Therap.*, 36 (1929), 569) injecting several cats and dogs with repeated doses of 1 to $1^1/_2$ mg. per kilo, at intervals of an hour, found the following average rises of pressure expressed in percentage of the original blood pressure; 1st injection, 30 per cent; 2nd injection, 26 per cent; 3rd injection, 22 per cent; 4th injection, 19 per cent; 5th injection, 19 per cent.

Pittenger (JOUR. A. PH. A., 17 (1928), 634) suggested that the mydriatic

action might be utilized in quantitative analysis, but apparently no work along this line has been published. In a quantitative study of the effect of 2 drops of 10 per cent ephedrine in a series of normal caucasians, Chen (*J. Pharmacol. & Exper. Therap.*, 33 (1928), 237) saw increases in pupil diameter varying from 0.8 mm. to 3.3 mm. in 10 individuals. This illustrates the variability of the response in man.

Three methods of biologic assay of ephedrine have been suggested, all of which are designed to overcome the interfering effect of tachyphylaxis.

Feng and Read (JOUR. A. PH. A., 16 (1927), 1034) made use of the pressor action, taking advantage of the small amount of tachyphylaxis induced by small doses given at long intervals. They gave intravenously 1 mg. per dog at hourly intervals, but apparently did little work with the method and report only one test. A dog weighing 5.2 kilos anesthetized with luminal was given at hourly intervals, 1 mg., 1 mg., 0.5 mg. and 2 mg. They do not state the pressor responses but give a reduced tracing showing the following rises on the reproduced tracing; 5 mm., 5 mm., $2^1/_2$ mm. and 7 mm.

Rowe (JOUR. A. PH. A., 16 (1927), 912) had previously studied the quantitative relationship between the pressor actions of epinephrine and ephedrine, and between the effects of the latter as given by intravenous injection and by mouth. His figures are, however, disturbed by the fact that he apparently did not recognize either the decreased action of ephedrine on repeated injection, or the increased action of epinephrine after ephedrine. In some cases he injected one first, in other cases the other, and he unites all results in a table showing a relationship varying from 1:100 to 1:1000.

Pittenger (JOUR. A. PH. A., 17 (1928), 634) checked Feng and Read's method on ten dogs and found that injection of 1 mg. caused enough tachyphylaxis to render the method untrustworthy. He suggests, as already noted, use of the mydriatic effect but reports no work with it.

To avoid the discrepant results due to individual differences, Chen (*J. Pharmacol. & Exper. Therap.*, 33 (1928), 237) suggested that each dog be "standardized" by determining its sensitiveness to epinephrine, and that the pressor effect of a single dose of ephedrine be compared to the pressor effects of a series of graded doses of epinephrine given previously. The strength of a given sample of ephedrine is thus expressed in terms of its relation to epinephrine. He believed that as epinephrine and ephedrine produced their pressor effects by a somewhat similar mechanism, animals should vary in their response to each of them to the same extent.

Our laboratories have been making an extensive study of certain compounds related to ephedrine and it was necessary during one phase of our work on one of them, phenylpropanolamine, briefly known as propadrin, to develop a method of biologic assay which would give quantitative results within 10 or 20 per cent.

We tried four methods: 1. The mydriatic action on the isolated frog's eye. 2. The action on the isolated uterus of the guinea pig. 3. The method used by Chen, modified by employing dogs anesthetized by chloretone, instead of pithed cats. 4. The method of Feng and Read, using similarly anesthetized dogs.

1. MYDRIATIC ACTION.

We can dismiss this method in a few words, by saying that although mydriasis was caused by all dilutions of propadrin down to 1:8000 (the weakest used), there was no relation between the strength of the solution and the degree of mydriasis. It was found that solutions of 1:8000 might cause more dilatation than 1:4000, and these more than 1:2000, even when the comparison was made between the two eyes of the same frog. Tests were conducted on 8 pairs of eyes, and the results were so unpromising that further work did not seem justified.

2. ACTION ON THE ISOLATED UTERUS.

Chen (*J. Pharmacol. & Exper. Therap.*, 33 (1928), 237) states that the action of ephedrine on the isolated uterus of the guinea pig does not lessen with repeated applications; on the other hand, Curtis (*J. Pharmacol. & Exper. Therap.*, 35 (1929), 333) found that there is lessened response in both the cat and guinea pig uterus, and this agrees with our own experience, with propadrin on the organ of the guinea pig. Figure 1, illustrating the response of the isolated uterus to re-

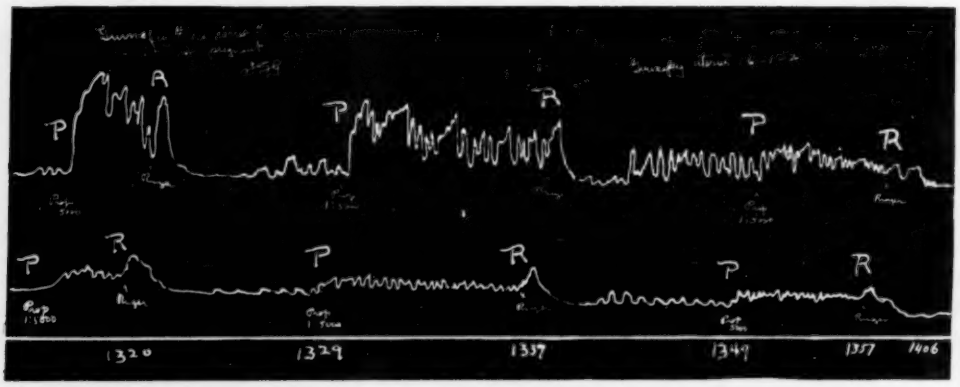

Fig. 1.—Isolated adult Guinea Pig uterus. Effect of repeated doses of same concentration of propadrin on two strips from the same uterus. At "P" propadrin 1:5000 wasadded to the bath. At "R" it was replaced by Ringer solution.

peated applications of the same concentration of propadrin, shows both the lessening response and the irregularity of the reduction. The method does not seem promising for quantitative studies.

3. PRESSOR RELATION TO EPINEPHRINE.

In testing out the method proposed by Chen we found that different dogs vary markedly in their response to ephedrine and propadrin. Thus, in a series of 40 dogs given doses of the latter varying from 55 to 1600 mg. per kilo, no quantitative relationship was found between dose and effect. For example, the 1600 mg. dose caused a rise of only 30 mm. of mercury, while another dog given only 390 mg. per kilo showed a rise of 110 mm. Five doses of 570 to 610 mg. per kilo, given to 5 different dogs, caused rises of, respectively, 20, 26, 32, 51 and 64 mm. The relation was no more exact by calculating the rise in terms of per cent of the original blood pressure. The same discrepancy between dose and effect, due to

variations in responsiveness in individual animals has been noted by other workers both with epinephrine and with ephedrine.

In the tests made on atropinized dogs, anesthetized with chloretone and morphine, we found a relationship of epinephrine to ephedrine varying from 1:120 to 1:1100 in 12 dogs, with an average of 1:495. Using 42 dogs in the same test with propadrin, the relation varied from 1:125 to 1:1000, the average being 1:495, the same as for ephedrine.

Our results would thus give ephedrine a much lower activity as compared to epinephrine than that found by Chen on pithed cats, but much higher than recently reported by Hasama (*Arch. exptl. Path. Ther.*, 153 (1930), 161) who found a relation of 1:3200 in rabbits.

If we take the average rise of pressure caused by a given dose of epinephrine and divide the dogs into two groups according to whether they were above or below average susceptibility and do the same with the response to propadrin, we find that of 40 dogs, 29 varied in the same direction, that is, they were above or below average susceptibility to both drugs, while in 11 the susceptibility to one drug was above average, that to the other below. Further evidence in this same direction, showing a lack of relation in susceptibility to the two drugs, is given by the fact that if we select the 7 dogs which were most susceptible to epinephrine, as shown by their giving a rise of pressure of 90 mm. or more from a dose of 20 mg. of epinephrine, the average relationship of propadrin to epinephrine was 1:738 as compared to 1:495 for the whole group. This shows that undue susceptibility to epinephrine does not extend to propadrin. Similar figures are found with ephedrine.

In some animals which seemed to be unduly deeply anesthetized by the chloretone, and in which the original blood pressure was very low, the response to ephedrine or to propadrin seemed to be more reduced than that to epinephrine. This does not account for the lower relative effect of ephedrine in our anesthetized animals as compared to Chen's pithed animals, as relationships as low as 1:1000 were found in a small series of pithed dogs.

The wide discrepancy found by Chen in a series of only 6 animals (relations varying from 1:133 to 1:294) shows that with pithed animals also, a very large number is required to obtain accurate quantitative results with any one sample.

4. EFFECT OF REPEATED DOSES ON BLOOD PRESSURE.

Not having obtained satisfactory results by the method just described, we turned to the earlier method of Feng and Read. The results were more satisfactory, but still leave much to be desired. By the method described below it was possible to obtain results within 20 or even within 10 per cent with only one or two dogs on each test. The method is as follows:

Anesthetized dogs are given repeated doses of ephedrine or propadrin intravenously, at intervals of an hour. Each dose contains 1 mg. of a standard solution or an approximately equal amount of the solution under test. The dose is not adjusted to the weight of the dog, as we found no relation between this and the response to a fixed dose. Large dogs are almost if not quite as likely to give a considerable rise as are small ones. The dog is first given 1 mg. of the standard preparation, and the rise measured. At the end of an hour it is given the solution

under test, and at the end of another hour the standard once more in the same dose. In this way we continue at hourly intervals until, preferably, four doses of each have been given. The averages of all the doses of each sample are then taken. If there be a discrepancy of more than 20 per cent between them, it can be fairly safely concluded that this represents a real difference in the potency of the solutions. In some dogs the rise from the first injection is unduly large, and in such cases this rise is excluded in casting the averages. Quite satisfactory results may be obtained if only half an hour is allowed between doses, but the hourly interval is probably best.

A few illustrative protocols will serve to show the kind of results obtained by this method.

Dog No. 168. Weight, 7.3 kilos. Comparison of two 1 per cent solutions of the same lot of propadrin, marked, respectively, No. 3 and No. 18.

Time.	Injection No.	Dose, Mg.	Rise, Mm.
10.55	18	1	22
11.55	3	1	12
13.00	3	1	12
14.00	18	1	10
15.00	18	2	14
16.00	3	2	14

The first rise was unduly high and is, therefore, omitted in calculating averages.

Average of other injections of No. 18—13 mm.

Average of all injections of No. 3—12 mm.

The result is within 10 per cent, the solutions are, therefore, of approximately the same activity.

Dog. No. 183. Weight, 8.15 kilos. Repeated injections of same solution of propadrin.

Time.	Injection No.	Dose, Mg.	Rise, Mm.
10.10	3	1	24
10.40	3	1	18
11.40	3	1	16
12.40	3	1	14
14.05	3	1	16
14.55	3	1	16
15.45	3	1	18
16.15	3	1	14
16.45	3	1	14

Disregarding the first aberrant response, we take every alternate rise and cast an average. The sum of the 2nd, 4th, 6th and 8th is 64 mm.; the sum of the 3rd, 5th, 7th and 9th is 62 mm. The averages being 16 mm. and $15^1/_2$ mm., a variation of only 3 per cent.

Dog No. 170. Weight, 9.1 kilos. Morphine, chloretone, atropine anesthesia. Comparison of two solutions of standard propadrin. A contains 10 mg. per cc.; B, 8 mg. per cc.

Time.	Injection.	Dose, Cc.	Rise, Mm.
11.40	B	0.1	6
12.10	A	0.1	12
12.50	B	0.1	8
13.20	A	0.1	10
13.50	B	0.1	10
14.20	A	0.1	14
15.48	B	0.1	14
16.21	A	0.1	12

Average rise from A 13½ mm.; from B, 10 mm., showing a distinct variation in activity in favor of A.

Dog No. 172. Weight, 5.5 kilos. Morphine, chloretone, atropine anesthesia. Comparison of three solutions of standard propadrin. A contains 8 mg. per cc. B contains 6.7 mg. per cc. C contains 5 mg. per cc.

Time.	Injection.	Dose, Cc.	Rise, Mm.
11.00	A	0.1	14
11.40	B	0.1	12
12.27	C	0.1	6
14.30	A	0.2	10
15.00	B	0.2	8
15.30	B	0.2	10
16.00	C	0.2	6
16.30	B	0.2	12
16.55	A	0.2	12

Average rise from 1 injection of 0.1 cc. and 2 of 0.2 cc. A, 12 mm.; B, 10⅔ mm.; C, 7½ mm. Showing that A is stronger than B and this than C.

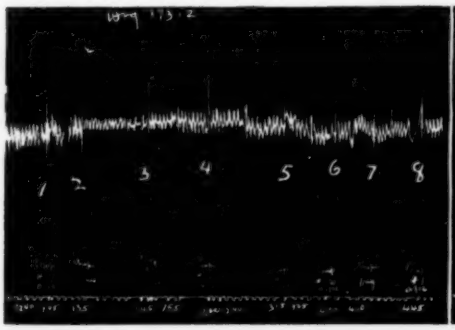

Fig. 2.—Dog 175. See Protocol.—Effect on blood pressure of small repeated doses of propadrin. Intravenous injection given as follows: 1, 12.45 propadrin No. 7, 0.1 cc. 2, 1.35 atropine. 3, 1.45 propadrin, No. 1, 0.1 cc. 4, 2.30 propadrin No. 6, 0.1 cc. 5, 3.15 propadrin No. 1, 0.1 cc. 6, 4.00 propadrin No. 6, 0.1 cc. 7, 4.10 atropine. 8, 4.45 propadrin No. 1, 0.1 cc.

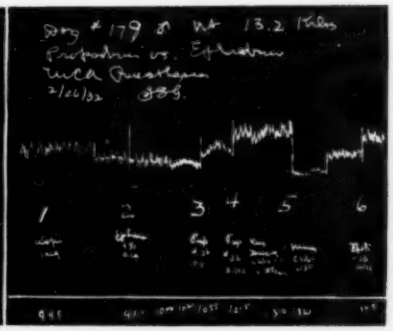

Fig. 3.—Dog 179. See Protocol.—Effect on blood pressure of small alternate doses of ephedrine and propadrin. Intravenous injections given as follows: 1, 9.40, atropine. 2, 9.50, ephedrine, 1%, 0.1 cc. 3, 10.55, propadrin 1%, 0.1 cc. 4, 12.45 propadrin, 1%, 0.1 cc. 5, Dog moving. Gave ether. 6, 1.45 ephedrine, 1%, 0.1 cc.

These few protocols will show the general character of the results obtained by this method, and that, even with only one or two animals it is accurate to within 20 or perhaps even 10 per cent. It is necessary to give repeated injections of each sample, and to take the average of the rises obtained, as there is always some variation in the rise from the same dose. The results are probably better if an hour is allowed to elapse between injections, although quite good results may be obtained with an interval of half an hour. If the rise obtained from 0.1 cc. of a 1 per cent solution is not more than 15 mm., doses of 0.2 cc. may be given, and will give a better contrast.

Quantitative studies, both by determining the pressor relation to epinephrine and by comparing the repeated effect of small doses, were made to determine the

stability of propadrin and ephedrine in 1 per cent solution in distilled water. Certain of these samples were subjected to influences, such as passing oxygen through the solution for 2 hours, incubation at 37° C. for 7 days, autoclaving for 50 minutes at 120° C. Of the lots subjected to each of these treatments, some samples contained possible protective agents including glucose, lactose, a trace of the free base and an antiseptic, S. T. 37 solution containing hexylresorcinol. Neither ephedrine nor propadrin solutions showed any loss of activity when subjected to the above treatments. The presence of protective agents was found to be unnecessary and the solutions associated with hexyl-resorcinol were not affected either by exposure to high temperatures or to oxygen.

The following protocol is typical of the results obtained. Solution No. 1 had been kept in the refrigerator: No. 7 was heated at 120° C. for 50 minutes; and No. 6 was incubated at 37° C. with hexyl-resorcinol (S. T. 37) solution.

Dog No. 173. Weight, 10.5 kilos. Morphine, chloretone, atropine anesthesia. Comparison of standard, sterilized and incubated samples of propadrin (Fig. 2).

Time.	Injection Propadrin Solution.	Dose, Cc.	Rise, Mm.
9.53	1	0.1	50
10.15	7	0.1	40
10.45	1	0.1	32
11.15	7	0.1	24
11.45	1	0.1	14
12.45	7	0.1	34
13.45	1	0.1	26
14.30	6	0.1	32
15.15	1	0.1	24
16.00	6	0.1	24

Although there is some lessening of effect from each of the first 5 injections given at intervals of only half an hour, this is adjusted by giving alternate injections and recovery of effect is seen when the interval is lengthened to one hour. Averaging the effects of each sample we find: No. 1, average 29 mm. No. 7, average $32^2/_3$ mm. No. 6, average 28 mm.

These results show that neither No. 6 nor No. 7 is appreciably weakened by the treatment to which it has been exposed.

It has already been mentioned that propadrin and ephedrine showed the same relative pressor action when compared to epinephrine. This finding was confirmed by two tests in which 1 mg. per dog of each were given alternately and the resulting rises of pressure compared. The protocols follow:

Dog No. 179. Weight, 13.2 kilos. Morphine, chloretone, atropine anesthesia. Comparison of 1 per cent solutions of ephedrine and of propadrin (Fig. 3).

Time.	Injection, %.	Dose, Cc.	Rise, Mm.
9.52	Ephedrine 1	0.1	24
10.55	Propadrin 1	0.1	22
12.45	Propadrin 1	0.1	24
13.45	Ephedrine 1	0.1	22

Average rise from ephedrine, 23 mm. From propadrin, 23 mm.

Dog No. 177. Weight, 11.8 kilos. Morphine, chloretone, atropine anesthesia. Comparison of 1 per cent solutions of ephedrine and of propadrin.

Time.	Injection, %.	Dose, Cc.	Rise, Mm.
9.55	Propadrin 1	0.1	22
10.45	Ephedrine 1	0.1	18
11.30	Propadrin 1	0.1	12
12.30	Ephedrine 1	0.1	12
13.30	Propadrin 1	0.1	12
14.50	Ephedrine 1	0.1	12

After the first two injections the effects agree exactly. Even including them, the ephedrine effects average 14 mm., the propadrin 15½, the results being within 10 per cent.

These protocols illustrate the close agreement in quantitative action and stability of propadrin and ephedrine.

SUMMARY AND CONCLUSIONS.

1. Of the four methods used for the quantitative physiologic assay of propadrin and ephedrine, namely, the effect on the pupil, the effect on the isolated uterus, the comparison of the pressor action with that of epinephrine and the comparison of the pressor action with that of a standard solution of the same drug, only the last was found to be suitable.

2. By the method described, assays can be made on one or two dogs with an accuracy of 20 or even of 10 per cent.

3. Propadrin is of approximately the same activity as ephedrine and is equally stable in solution.

A STUDY OF SENECIO RIDDELLII.*

BY F. S. BUKEY AND R. W. CUNNINGHAM.[1]

PART 1.

INTRODUCTION.

A number of Senecio such as *S. integerrimus, S. riddellii, S. vulgaris, S. ilicifolius, S. burchellii, S. latifolius, S. jacobœa, S. aureus, S. præcox, S. canicidia, S. albicaulis, S. grayanus, S. cervariæfolius* and many others, have been found in many parts of the world. *Aureus* is official in the N. F. V and has enjoyed some use as a drug. It was employed by the Indians as a vulnerary and later was used as an emmenagogue. Some of the above-mentioned species have been used as purgatives, emetics and internal hemostatics, although of doubtful value in most cases.

It has been found that some of these species are poisonous to animals. Debrierri (1) reports the poisonous effects of canicidia on dogs. Gilruth (2), (3), (4), (5), (6), (7), (8) proved the toxicity of *S. jacobœa* in producing cirrhosis of the liver (Winton disease) in horses of New Zealand. Chase (9), Robertson (10), Dixon (11) and Theiler (12), (13) succeeded in proving *S. latifolius* and *S. burchellii* to be the cause of hepatic cirrhosis or Malteno disease of South Africa. Stockman (14), Thompson (15), Craig and Kehoe (16), Stanley (17), Knowles (18), Leychon (19), Reeks (20) and Rutter (21) all report cases of poisoning by *S. jacobœa* among the

* Scientific Section, A. PH. A., Toronto meeting, 1932.

[1] The authors wish to express their thanks to Dr. L. Van Es of the department of Animal Pathology, University of Nebraska, for his coöperation and assistance in this study.

live stock of the British Isles. As a result of their work, the government made provisions for the extermination of the plant (22).

Wilmott and Robertson (23) in 1920 give an interesting report of a number of cases of hepatic cirrhosis in man. They attribute the disease to the presence of seeds and other parts of *S. burchellii* and *S. ilicifolius* in the wheat used for bread making. The disease required from three weeks to two years to run its course. Nearly always death resulted. The malady produced nausea, vomiting and severe abdominal pain, with occasionally diarrhea and passing of blood. Post mortem disclosed a discolored cirrhotic condition of the liver and in some cases ulcers of the digestive tract were noted.

Pictou disease of Canada, an enzootic liver disorder affecting cattle, was found to be caused by *S. jacobœa* (24), (25), (26), (27), (28), (29), (30).

German investigators (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45) describe an enzootic liver disorder of horses called "Schweinsberger disease" leaving scarcely any doubt but that it is similar to enzootic disorders mentioned in the other parts of the world.

In 1912 and succeeding years, western Nebraska ranchers reported great losses among horses from a new disease in these parts which became known as "walking disease." Adjacent parts of Colorado and Wyoming reported similar losses. It has been reported from the Pacific Northwest (32). A similar disease known as "bottom disease" was once prevalent in the Missouri valley and was described by Schroeder (33) and Smith (34) in 1893. The area concerned in Nebraska is table land of sandy loam soil having an altitude of 4000 to 5000 feet. The climate is characterized by relatively low rainfall (17 inches per annum) and free wind movement. This being a stock-grazing section, these losses from "walking disease" became of great economic importance.

The disorder in this section affected horses chiefly, although a few cases were reported among cattle (Van Es (31)). The affected animal separates from the others and becomes sluggish and drowsy. Usually the appetite fails and may become perverted. The animal may chew at the mangers, or eat dirt. This habit, and the manner in which affected animals push themselves against objects, are likely responsible for the bruises and lacerations about the mouth and head.

In the more advanced stages, there are signs of abdominal pain, general depression and inability to coördinate movements. Standing and walking are difficult and are accompanied by staggering. The animal's fetlock joints knuckle over and he stands with feet apart. Nervous disorders are also exhibited in the tendency of the animal to wander aimlessly about, walking through fences or over the rim of a canyon, hence the name "walking disease." There is a marked loss of weight and animals are very weak in the later stages. The course of the disease averages about four weeks.

Autopsies performed by Dr. Van Es and his co-workers established the liver as the chief point of attack. This organ was discolored and usually presented a pale brownish to a blue-gray cast. The whole organ was mottled in appearance. The tissue was more firm than normal tissue and resisted the knife. Upon histologic examination he found a typical necrobiosis. Much functioning tissue had been destroyed resulting in scar tissue and enlargement of many cells in an effort of com-

pensatory hypertrophy. All stages of destruction and hypertrophy were noted. Nearly all cases exhibited conspicuous hepatic hemorrhages.

Liver disturbances of this nature are not uncommon in higher mammals. Among the intoxicants capable of injuring liver cells and setting up reparative processes are spoiled foods, toxins from certain infections, poisonous plants, phosphorus, arsenic and others.

The work of investigators in other parts of the world casts suspicion upon plants and more specifically upon the *Senecios*. "Walking disease" of Nebraska showed marked resemblance to other diseases caused by the *Senecios*. Van Es (31) reports that samples of diseased livers obtained from certain other countries were identical in the character of the lesions with those produced by the investigators in Nebraska.

As the etiologic relationship of *Senecio* to enzootic liver disorders was well established in other parts of the world, it was strongly suspected here. Two species are found in the region involved: *S. integerrimus* and *S. riddellii*. Van Es (31) reports that feeding experiments with the former showed no evidence of liver lesions as produced in "walking disease." However, such experiments carried out with *S. riddellii* gave positive results.

S. riddellii is a perennial with a long tap root, from the crown of which arises a branched, very leafy stem from 12 to 24 inches in height. The leaves are from 1 to 3 inches long, and are pinnately parted into 3 and 9 narrow filiform segments. Each branch ends in a corymb of 8 to 20 flower heads. The plant is typically an arid type.

Kelly and Lynn (46) report the presence of alkaloids in *S. aureus*. Grandval and Lajoux (47) working on *S. vulgaris* describe two alkaloids present which they call senecionine and senecine. Müller (48) isolated an alkaloid, fuchsisenecionine from *S. fuchsii* and another from *S. sylvaticus*. Watt (49), (50) in 1909 extracted two alkaloids, *senecifolins* and *senecifolidine* from *S. latifolius*. Cushny (51), (52), (53), (54) found that these alkaloids were toxic and experimentally produced symptoms comparable to those found in the field cases of poisoning among horses. He concludes that enzootic liver disease among horses reported from Africa, Canada and New Zealand was probably caused by these or similar toxic principles in some specie of Senecio.

It can be concluded from the foregoing discussion that several of the *Senecios* contain toxic principles. The work of Dr. Van Es has shown *riddellii* to be toxic to horses. The literature apparently contained no account of experimental work having been done upon the toxic principle of this species. This paper constitutes the first part of a study being carried out upon the isolation and identification of this substance, and the determination of its physical, chemical and pharmacological properties.

EXPERIMENTAL.

The material for this problem was gathered in Scotts Bluff county, Nebraska, during the latter part of June 1931. This was several weeks previous to the time of flowering. The plants were air dried and the leaves and stems separated from the roots before grinding. The material was ground in a disintegrator so that all of it would pass through a 40-mesh sieve.

The percolator used in extracting the material was made from a ten-gallon cream can. A hole was drilled in the bottom of the can and a three-eighths inch pipe and stop-cock were welded into this opening. This made an ideal percolator as the top might be closed during maceration, diminishing the solvent loss.

About twenty pounds of the ground leaf and stem material were packed in the percolator and macerated with ether for twenty-four hours. The ether was then drawn off and the process repeated. At the end of the third extraction most of the waxes and the color had been removed. The ether was reclaimed for other extractions. The residue was a deep green waxy substance. Without drying the material in the percolator, hot ninety-five per cent alcohol was added and the above procedure repeated until the plant was exhausted. This required from four to five extractions for completion. Eighty per cent of the alcohol was next removed from the extract under reduced pressure, keeping the temperature under 70° C. for several days. The concentrated extract was placed in an evaporating dish and, on exposure to the air for several days, brown crystals formed. Several crops of these were obtained on further standing. These crystals, on repeated recrystallization from hot absolute alcohol, gave a buff-colored powder which had a m. p. 156° C.

The residue from the crystallization was a black tarry mass which became solid in a few days. This material was found to be insoluble in both water and alcohol in which it was formerly quite soluble. Further work is in progress on this material to determine its composition.

Through the coöperation of Dr. Van Es of the department of Animal Pathology, University of Nebraska, the toxicity of the substance melting at 156° C. was determined.

Two horses received daily an amount of the crystals approximately equivalent to 4 pounds of green plant. This quantity was comparable to the amount of green plant which gave positive results in previous experimentation by Dr. Van Es (31) in determining the cause of walking disease. Each horse received a total of 16 doses.

The substance of Dr. Van Es's report follows:

About ten days after beginning the feeding, the first horse showed a failing appetite. A gradual loss in weight was noted and in fifteen days' time the animal was manifestly ill. He refused feed and occasionally showed evidence of abdominal pain. He became stupid and died early on the twentieth day.

The second horse exhibited similar symptoms. This subject showed diarrhea and also presented symptoms of cerebral origin. On the twentieth day the animal staggered when induced to move, and had great difficulty in standing. Abdominal pain was evidenced. The subject died on the evening of the twentieth day of the experiment.

Post mortem examination upon both animals showed excessive abdominal fluid and great changes in the livers and kidneys. The liver was greatly enlarged and showed a mottled surface. There was evidence of hyperemia and hepatic hemorrhages.

Histologic examination of the livers of both animals indicate necrobiosis with the beginning of interstitial thickening. Necrosis was especially noted in one case. The kidneys showed severe nephrosis.

Dr. Van Es concludes as follows:

"The dry alcohol extract of *Senecio riddellii* was toxic to the two horses fed with it and caused their deaths. The intoxication produced, for so far as this can be measured by pathoanatomic observation of the livers, was more severe than that usually observed in field cases of 'walking disease.' We attributed this to the greater concentration of the intoxicant. The symptoms of the two horses are comparable to those seen in the field disorder and whatever differences observed were traceable to the manner in which the animals were kept.

"Renal involvements rarely seen in the field cases were, no doubt, caused by the excessive amount of the intoxicant used in the experimental horses. In our experiment with green plants the same phenomena could be observed (31).

"There is warrant for conclusion that the intoxicant factor in the dry extract is of the same character as that which causes the 'walking disease' of Northwestern Nebraska."

Due to the small quantity of the toxic substance present in *S. riddellii* it was necessary to extract large amounts, to satisfy the needs, in this type of animal experimentation. During the summer of 1931, more than 1200 pounds of the plants were collected. This represented a little over 300 pounds of dry material. In July 1932, an additional 1200 pounds of plants were collected. Most of the extract of the first collection was used for animal experimentation. With the toxic principle in a fairly pure state, work is in progress to determine its composition. Further study is being made as to the quantity of toxic principle present in the plant at various seasons of the year. It is thought by some that the young plants in the early spring are the most toxic. However, this point has not been definitely proved. Our next paper will constitute the chemical study of *S. riddellii*.

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A COMPARATIVE STUDY OF TWO XANTHINE DIURETICS.*

THEOPHYLLINE SODIUM ACETATE AND THEOBROMINE SODIUM SALICYLATE.

BY A. RICHARD BLISS, JR.,[1] AND ROBERT W. MORRISON.[2]

INTRODUCTION.

No reliable quantitative clinical experiments on the comparative diuretic effects of the various Xanthine derivatives in graduated doses have been reported in the literature, and, with the exception of one quantitative report in German and the reports of the authors of this paper, there are no published reports concerning the actions produced in laboratory animals by graduated doses of the newer Theobromine and Theophylline derivatives. This investigation was prompted by numerous inquiries concerning the diuretic powers of these agents, and this paper is the second of a series of reports concerning comparative studies of Theobromine and its derivatives "Theocalcin" (Theobromine Calcium Salicylate) and "Diuretin" (Theobromine Sodium Salicylate), and Theophylline and its derivatives "Phyllicin" (Theophylline Calcium Salicylate) and "Theocin Soluble" (Theophylline Sodium Acetate).

Although Xanthine possesses very little diuretic power, certain derivatives containing the Xanthine nucleus are among the most powerful of the diuretics. Of the dimethylxanthines Theophylline and Theobromine are the most active, while Caffeine is the most active of the trimethylxanthines.

Because of its pronounced central effects, Caffeine has been more or less supplanted as a diuretic by Theophylline and Theobromine which have not its strong central effects, and which are credited generally with more powerful diuretic actions. Some writers consider Theobromine to be more reliable in action and less prone to

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* Scientific Section, A. PH. A., Toronto meeting, 1932.

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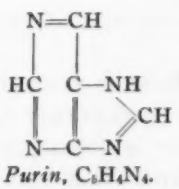
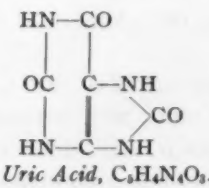
excite disagreeable nervous symptoms, although many claim that it is apt to be irritating to the kidneys. Theophylline is credited with being more prompt in producing diuresis, and its action is supposedly of shorter duration. It has little, if any, central stimulating action in the dosage usually employed, but the drug is said to be more irritating to the gastrointestinal tract and to the kidneys.

Theobromine, Theophylline and Caffeine may fail to produce a diuresis if there is no excess of water in the tissues, as with rabbits which have been kept for a long period on a dry diet. Apparently, these agents hasten the excretion of excess water (6). However, it has been found that Caffeine may fail to increase the secretion of urine even when water is at the disposal of the animal. Schroeder (12) in 1886 demonstrated that Caffeine invariably acts as a diuretic in rabbits providing the nerves going to the kidneys are first sectioned, or Chloral Hydrate or Paraldehyde are administered first to the animals, measures thought to prevent an interfering vasomotor stimulation. Diuresis is always obtained in the dog if the kidneys are first denervated or the vasomotors paralyzed, and section of the vagus nerves results in increased diuresis, or induces it when absent. These results have led to the conclusion that the vagus nerves carry inhibitory fibres to the secretory cells of the dog's kidneys, and that these fibres are stimulated by Caffeine (1). Theobromine, however, does not stimulate these vagus fibres, and this drug produces diuretic effects even when the nerves are intact (14).

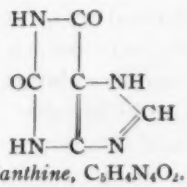
FORMULAS.



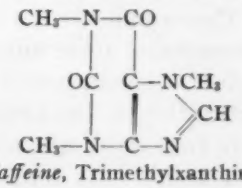
Purin, $C_5H_4N_4$.



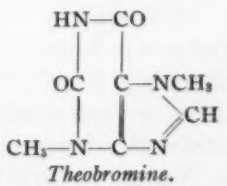
Uric Acid, $C_5H_4N_4O_3$.



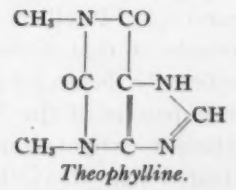
Xanthine, $C_5H_4N_4O_2$.



Caffeine, Trimethylxanthine.



Theobromine.



Theophylline.

Wallace and Pellini (19) demonstrated that Theophylline, Theobromine, Caffeine and "Diuretin" not only failed to produce a diuretic action in dogs kept on a fixed food and water intake, but instead showed a decided decrease in the daily output of urine which often amounted to 50% of the normal volume. Further, that the Sodium Chloride content was diminished also. These investigators suggested that there is a shift of water and Sodium Chloride from the circulating

blood into the tissues, and that Caffeine and its allies bring this about through the production of a dilatation and an increased permeability of the capillaries in the splanchnic organs and muscles, these effects overshadowing the kidney action in animals which are in water balance. The diuretic effect, then, appears when there is an excess of water in the body or when the tissues give off some of their stored water.

The effects of Theobromine on the kidneys are stated generally as being practically identical with those of Caffeine. Solis-Cohen and Githens (15) claim that Theobromine differs from Caffeine in not stimulating the vasomotor and the inhibitosecretory nerves of the kidney, and that it consequently produces diuresis constantly in rabbits and dogs. Sasaki (10) found that the continued administration of Theobromine increased water excretion in rabbits only when these animals were kept on a wet diet; but that chloride excretion is increased also on a dry diet, *i. e.*, independently of a diuretic action. "Diuretin" (Theobromine Sodium Salicylate), "Agurin" (Theobromine Sodium Acetate) and other double salts of Theobromine have been widely employed in the place of the free substance itself because of their greater solubility in water.

Hellin and Spiro (5) found that Caffeine is effective in pure tubular nephritis but that it fails in glomerular and general nephritis. They reported that Theophylline and Theobromine are more effective. Pearce, Hill and Eisenbrey (8) and Schlayer and Hedinger (11) have confirmed these observations. Some consider these findings as important evidence that the diuretic effect of Caffeine is exerted on the glomerular circulation and filtration, and not on the tubular epithelium.

Sollmann and McComb (16) report that Caffeine in ordinary doses does not appear to produce any demonstrable injury even in nephritic subjects, but that in larger doses it may increase albuminuria. They advise against the continued use of Theophylline even in moderate doses. Miller (7) is of the opinion that Theophylline and Theobromine may cause gastric and renal irritation. Chevalier (3) reports the presence of toxic impurities in commercial samples of Theobromine. Emerson (4) observed no increased albuminuria in acute or chronic nephritis following the administration of Theobromine. Pouchét and Chevalier (9) claim that the Theophylline in large doses will injure glomerular and tubular epithelia.

Vieth and Leube (18) determined the most effective daily doses of Theobromine, "Diuretin," "Phyllicin," "Theocalcin," et cetera, in rabbits. These investigators concluded that of the acid groups introduced in position 1 of the Theobromine molecule only the acetyl group increased diuresis. Bürgi's (2) assumption that the diuretic powers of the Xanthine derivatives are enhanced by salts was confirmed by these investigators in their experimental work with certain salicylates. They demonstrated that the Calcium salts of the Xanthine derivatives may influence diuresis in rabbits if this metal is combined with Salicylic Acid.

In human patients, Stewart (17) observed that Theobromine Calcium Salicylate was less irritating to the stomach than Theophylline and Theobromine Sodium Salicylate; and that this drug may be administered daily for months without untoward symptoms. Selig (13) is the only writer who has reported the effect of Theobromine Calcium Salicylate on the volume of urine excreted by man. He observed that this agent induces diuresis.

ANIMAL EXPERIMENTATION.

The series of experiments herewith reported were carried out on adult rabbits which were kept on a complete and balanced diet determined for the individual animal. The daily water-intake was carefully controlled. The animals were housed in individual metabolic cages. New animals were used for each dose series. Before beginning the administration of the drugs, the animals were observed over a period of days to establish whether they were in a state of metabolic equilibrium. The drugs, in aqueous solution or mixed with water, were administered three times a day (morning, noon and evening) by stomach tube over a period of four days and the observations continued thereafter until the daily output approached that of the premedication period. The daily observations included the total volume of urine voided, the determination of the physical characteristics of the urine, reaction, specific gravity, total solids, uric acid, urea, albumin, sugar and microscopic examination.

RESULTS.

The tables which follow give the observations made and the results obtained in this series of experiments with Theophylline Sodium Acetate ("Theocin Soluble") and Theobromine Sodium Salicylate ("Diuretin").

The first table (Table I) represents the type of daily record which was kept for the individual animal.

Tables II and III present the average percentages of increase and decrease in the urine volume output for the medication periods, the average percentages of increase calculated from the maximum 24-hour urine output during the medication periods, the average percentages of increase in solids, also in uric acid, the increase in albumin, also in sugar, the duration of diuresis, and the days during which the higher 24-hour output occurred.

DISCUSSION.

It should be stressed that the drugs were not administered until long observation had established that the rabbits were in good balance as determined by intake, output and weight, and that the animals were kept on a fixed daily food and water intake.

A study of the tables makes it obvious that in rabbits:

First: Relatively small doses of "Theocin Soluble" and "Diuretin" are capable of producing a good diuresis, an appreciable increase in the solids and the uric acid outputs, and a diuresis of fair duration.

Second: Thirty (30) mg. per Kilo three times a day is the most efficient dose of "Theocin Soluble," if judged from the standpoint of the increased volume of urine output during the medication period, the increase in solids, the increase in uric acid eliminated, and the duration of the diuretic action. The average duration of the diuresis for the various doses listed is 6.35 days, the minimum being 5 and the maximum 7.25.

Third: No evidence of local irritation was obtained with "Theocin Soluble" until doses of 50 mg. or more per Kilo three times a day were reached. Gastroenteritis and renal irritation were observed in the animals that died.

TABLE I.—DIURETIC EFFECTS OF CERTAIN XANTHINES ON RABBITS.

Uniform Fluid Intake: 150 Cc. Daily. Drug Given on 5th through 8th Days.

Animal.	Drug and Dose Gm. T. i. d.	Day.	Total Daily Output.	Color Turb. React.	S./G.	Total Solids Gm. p. Cc.	Uric Acid Gm. p. L.	Urea Gm. p. Cc.	Album Gm. p. L.	Sugar %.	Micro-scopic.	Other Abnormalities.
1	Normal Pre-med.	1	42	y/s/al	1.012	0.027	0.18	0.015	0.20	Neg.	Neg.	Neg.
		2	44	y/s/al	1.010	0.022	0.18	0.010	0.30	Neg.	Neg.	Neg.
		3	45	y/s/al	1.012	0.027	0.18	0.020	0.20	Neg.	Neg.	Neg.
		4	40	y/s/al	1.010	0.022	0.18	0.010	0.20	Neg.	Neg.	Neg.
	Averages		43	y/s/al	1.011	0.025	0.18	0.014	0.23	Neg.	Neg.	Neg.
	Diuretin 0.030 Gm.	5	80	y/m/ac	1.018	0.042	0.16	0.014	0.40	Neg.	Neg.	Neg.
	per Kilo	6	56	y/m/ac	1.014	0.033	0.18	0.014	0.30	Neg.	Neg.	Neg.
		7	62	y/m/ac	1.018	0.042	0.22	0.012	0.30	Neg.	Neg.	Neg.
		8	55	y/m/ac	1.010	0.022	0.25	0.010	0.20	Neg.	Neg.	Neg.
	Averages		63	y/m/ac	1.015	0.035	0.20	0.012	0.30	Neg.	Neg.	Neg.
	Post-medication	9	52	y/m/al	1.012	0.027	0.22	0.010	0.50	Neg.	Neg.	Neg.
		10	62	y/m/al	1.010	0.022	0.17	0.010	0.15	Neg.	Neg.	Neg.
		11	42	y/m/al	1.010	0.022	0.17	0.010	0.20	Neg.	Neg.	Neg.
		12	45	y/m/al	1.010	0.022	0.14	0.010	0.20	Neg.	Neg.	Neg.
	Averages		50	y/m/al	1.011	0.023	0.18	0.010	0.26	Neg.	Neg.	Neg.

y = yellow. s = slight turbidity. al = alkaline reaction.
m = moderate turbidity. ac = acid reaction. Pre-med. = pre-medication period.

Fourth: In the case of "Diuretin," 50 mg. per Kilo three times a day appears to be the most efficient dose from the standpoint of increased urine output, in increase in solids eliminated, and the increase in the elimination of uric acid. The percentage of uric acid eliminated was in direct ratio to the dose of the drug. The maximum uric acid output was obtained with 100 mg. doses. The average duration of diuretic action for the doses listed was 7.3 days, the minimum being 7 days and the maximum 8.25 days. Thus "Diuretin" shows a slight advantage over "Theocin Soluble." In promptness of diuretic action these two drugs appear to be about equal, action being observed in each case on the first drug day.

TABLE II.—EFFECTS OF VARIOUS DOSES OF THEOCIN SOL. ON RABBITS.

Dose Mg. per K. T. i. d.	Ave. % Increased Output.	Ave. % Increased Max. Op.	Ave. % Increased Solids.	Ave. % Increased Uric A.	Increased Albumin.	Increased Sugar.	Duration Diuresis through	Day(s) Maxim. Output.
10	33	72½	48	154½	..	..	6½ days	1, 3 drug; 1, 2 post
30	49	88	58½	189	..	..	6½ days	1, 3 drug; 2 post
50	35	96	34	164	Plus	..	5 days	1, 3 drug
75	64	120	36	260	Plus	..	7¼ days	1, 3 drug; 3, 4 post
			One animal died third drug day. Two animals lost weight during drug period.					
100	131	100	90	267	Plus	..	6½ days	1 drug; 2 post
			Two animals died during second drug day. All animals that died showed casts in urine, and gastroenteritis.					

NOTE: Columns one and two refer to the volume of urine. In the last column "drug" = medication day; "post" = post-medication day.

Fifth: Irritation was manifested with "Theocin Soluble" when this drug was administered in doses of 50 mg. or more per Kilo three times a day. "Diuretin," in doses up to and including 100 mg. per Kilo three times a day, did not produce any demonstrable irritation of the kidneys or of the gastrointestinal tract.

Sixth: No deaths occurred with "Theocin Soluble" until doses of 75 mg. or more per Kilo three times a day were administered.

Seventh: Both drugs produce an increase in the volume of urine voided, the amount of uric acid eliminated, and the quantity of solids in the urine. Within

TABLE III.—EFFECTS OF VARIOUS DOSES OF DIURETIN ON RABBITS.

Dose Mg. per K. t. i. d.	Ave. % Increased Output.	Ave. % Increased Max. Op.	Ave. % Increased Solids.	Ave. % Increased Uric A.	Increased Albumin.	Increased Sugar.	Duration Diuresis through	Day(s) Maxim. Output.
10	50	92	45	72	..	..	7 days	3, 4 drug; 1, 6 post
30	44	94	51	88½	..	..	8 days	1, 4 drug; 2, 4 post
50	57	97	52½	158	..	..	7½ days	3, 4 drug; 1 post
75	26	108	34½	215	..	..	7¾ days	1 drug; 2, 3 post
100	46	115	53	262	..	..	8¼ days	1 drug; 3, 4 post

what appear to be the more efficient safe doses in rabbits, "Theocin Soluble" seems to yield a higher uric acid output than "Diuretin;" but "Diuretin" is apparently more safe, as evidenced by the facts that there were no deaths among the "Diuretin" animals, and no evidence of renal or gastrointestinal irritation was observed. What proportion of the uric acid eliminated is derived from the drugs themselves, and the extent of the possible rôle of the Salicylic and Acetic Acid groups in the production of the diuresis have not been determined as yet.

The results obtained with Theophylline Calcium Salicylate, Theobromine Calcium Salicylate, Theophylline and Theobromine will be presented in other papers.

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MANGANESE PREPARATIONS FOR THE TREATMENT OF FUNGOUS INFECTIONS.*

BY F. A. TAYLOR.

Potassium permanganate has long enjoyed a vogue in the treatment of ring worm infections. As early as 1822 (1) manganese dioxide was introduced into therapeutics and since that time the number and uses of manganese compounds have steadily increased. In 1843 (2) the dioxide was prescribed in the treatment of herpes and scabies. It was said to be of value in the healing of old ulcers, as a depilatory and as a remedy for skin diseases, especially itch and porrigo. It was applied as an ointment.

From this beginning, stimulated by the anticipated value of permanganate as an antiseptic, the modern use of the salt in fungous infections may be said to have arisen.

Some of the considerations which have limited the use of permanganate as a

* From the William H. Singer Memorial Research Laboratory of the Allegheny General Hospital, Pittsburgh, Pa.

bactericide are of as great importance in limiting its action on fungi. The salt is promptly reduced by organic matter, especially such susceptible matter as occurs in the fluids of organisms. Since the reduction gives rise to the insoluble manganese dioxide, only the lowest concentrations of the element may be attained. Contact with the fungi, deeply embedded in the skin, may be the result of colloidal dispersion or of the reduction of the oxide and salt formation. In any event the favorable effect would seem to be due not specifically to the permanganate molecule or ion but rather to the manganese. A manganous salt might be much more effective. It should be mentioned that manganous hydroxide is a protein precipitant.

A trial was made of the action of manganous sulphate, at a dilution of 1:1000 in water, on fungous infections of the foot. The manganous salt produced much more striking improvement than did permanganate. In no case of infection of the foot did it fail to cause at least a temporary disappearance of the lesions.

Since, conceivably, the lipins of the skin might protect the organisms from contact with this water-soluble salt, it was thought that an oil-soluble preparation would be advantageous. For this purpose manganous oleate was dissolved in anhydrous lanolin and applied to the skin. As an alternative the manganous salt of the mixed fatty acids of olive oil were employed. This treatment also was effective in foot infections.

Curiously enough these preparations were quite ineffective in infections of parts of the body other than the foot.

The manganous salts were prepared by double decomposition, in alcoholic solution, between manganous chloride (1 mol.) and the potassium salts of the fatty acids (2 mols.). The quantitative yield indicated that the composition was approximately Mn:2 acid. The salts were washed with water and with acetone and dried at room temperature. They were light flesh colored.

The manganous salt (10 per cent) dissolved readily on stirring in warm anhydrous lanolin. A further improvement in the ointment was obtained with the introduction of a water-soluble salt in addition to the oil-soluble one. An aqueous solution (10 per cent) of manganous chloride or sulphate was dispersed in the lanolin solution in a concentration of 10 per cent.

Other aspects of the work will be offered for publication in the proper place.

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Peter Valaer states in *Journal A. M. A.*, May 6, 1933, "the discovery of triorthocresyl phosphate was made by the chemists of the Bureau of Industrial Alcohol and was turned over to the Public Health Service for physiologic tests to determine whether the substance that was found in the adulterated ginger was the ingredient that actually produced paralysis in more than 30,000 cases throughout the United States. It was this laboratory which first determined it quantitatively in numerous samples, and some of this isolated substance was turned over to the Public Health Service for physiologic tests."

A METHOD FOR THE QUANTITATIVE DETERMINATION OF MINUTE AMOUNTS OF PEROXIDES IN ETHER.*

BY L. W. GREEN AND R. E. SCHOETZOW.

The U. S. P. X test for peroxides in ether is a qualitative one which requires that a 10-cc. sample, treated with cadmium-potassium-iodide T.S., must not produce a color within one hour. It will not reveal the presence of small amounts of peroxides. In view of the importance of freedom from peroxides in anesthetic ether, it appeared desirable to develop a quantitative and more sensitive method.

After consideration of various published methods and modifications of the U. S. P. method, by increasing the size of sample, providing a homogeneous solution for reaction rather than two phases and acidification, we reached the conclusion that a modification of the U. S. P. method based on the above points would yield the desired result. Accordingly, the method given below was developed and found, by extended laboratory application, to give satisfactory results. It will reveal and measure ether peroxides in quantities less than 1 part per million.

METHOD.

Place 100 cc. of the ether under examination in a 250-cc., glass-stoppered flask. In a similar flask, conduct a blank determination, omitting the ether sample. Add 20 cc. of absolute alcohol and mix. Then add a freshly prepared solution of 1 Gm. of cadmium and potassium iodide in 5 cc. of 36% acetic acid. Mix thoroughly and allow to stand in the dark for one hour. Observe the flasks in a good light against a white background, and, if any yellow color is visible titrate with *N*/50 sodium thiosulphate without the use of starch T.S. Toward the end of the titration, stopper the flask and shake vigorously. Before again opening the flask cool under running water. Vigorous shaking is important if one is to avoid passing the end-point, since two layers are sometimes formed during titration.

Calculate results and express them in terms of parts per million of ethyl peroxide, "$(C_2H_5)_2O_2$."

Each cc. of *N*/50 sodium thiosulphate is equivalent to 9.008 parts per million ethyl peroxide.

The following precautions must be observed:

Use carbon dioxide free distilled water to prepare the *N*/50 sodium thiosulphate solution.

The solution of cadmium and potassium iodide in 36% acetic acid turns yellow on standing and must, therefore, be prepared just prior to its use.

Should cadmium and potassium iodide be precipitated, add a few drops of water, drop by drop, until it redissolves.

In developing this method, we conducted several series of determinations, varying each factor in turn while keeping the other factors constant. In this way experiment showed, that,

One gram of cadmium and potassium iodide was necessary,

The proper amount of 36% acetic acid was 5 cc.; a lesser amount was insufficient and a greater amount caused low results,

One hour was the minimum time for the complete liberation of iodine,

The effect of atmospheric oxygen was nil, and

Working under nitrogen was, therefore, unnecessary.

Finally, it was shown, by experiment, that the presence of acetaldehyde did not interfere.

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* Scientific Section, A. PH. A., Toronto meeting, 1932.

In order to determine the accuracy of the proposed method, we applied it to samples of ether containing varying amounts of ether peroxide. We first developed a high concentration of peroxide in ether by exposing it to sunlight and then aging. This peroxide ether was diluted with different amounts of an almost peroxide-free ether. The mixtures as well as the almost peroxide-free ether and the peroxide ether were then assayed for peroxides by the above method with the results recorded below.

Sample.	Cc. Peroxide-Free Ether.	Cc. Peroxide Ether.	Cc. *N*/50 Thio.	P. p. m. $(C_2H_5)_2O_2$ Found.	P. p. m. $(C_2H_5)_2O_2$ Calculated.
I	100	0	0.05	0.5	.....
II	75	25	7.99	71.9	71.4
III	50	50	15.99	144.0	142.8
IV	25	75	23.88	215.1	214.2
V	0	100	31.65	285.1	.....

The figures in the last column are calculated from the proportions of ether used and they agree closely with the results obtained by the proposed method.

The method for the determination of peroxides was also applied to minute amounts of aqueous hydrogen peroxide, as follows:

An approximately 0.03% hydrogen peroxide solution was prepared, and by the U. S. P. X assay method found to contain 0.00031 Gm. hydrogen peroxide per cc. Small amounts of this solution, measured in a micro burette, were then assayed by the proposed method. The results are given in the following table:

Sample.	Cc. 0.03% H_2O_2.	Cc. *N*/50 Thio.	P. p. m. H_2O_2 Added.	P. p. m. H_2O_2 Found.
I	0.25	0.240	0.8	0.8
II	0.75	0.610	2.3	2.1
III	1.25	0.985	3.9	3.4
IV	1.75	1.500	5.4	5.1
V	2.25	1.960	6.9	6.7
VI	2.75	2.405	8.5	8.2
VII	0.00	0.000	...	...

Parts per million of hydrogen peroxide as ethyl peroxide are calculated on the basis of a 100-cc. sample. In assaying Samples IV, V and VI, small amounts of glacial acetic acid were added to correct for the decrease in acidity caused by the water introduced with increasing amounts of aqueous hydrogen peroxide. Examining the above results, we find that the largest error in the six assays was one-half of one part per million, while the average error was only one-fourth of one part per million.

CONCLUSIONS.

1. A method for the quantitative determination of minute amounts of peroxides in ether has been developed.
2. This method is sensitive and accurate to less than one part per million of ethyl peroxide.
3. It is not affected by acetaldehyde or atmospheric oxygen.

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THE PREPARATION AND OPTICAL ROTATION OF PURE QUINIDINE.*

BY C. L. BUTLER[1] AND LEONARD H. CRETCHER.[2]

Quinidine is separated from the mixture of alkaloids extracted from cinchona bark after removal of quinine.[3] Since the hydrogenated derivatives of the four common cinchona alkaloids, quinine, quinidine, cinchonine and cinchonidine, also occur naturally, and since the solubilities of the reduced bases are quite similar to those of the unreduced substances, the preparation of absolutely pure alkaloids is sometimes exceedingly difficult. It is not surprising that ordinary commercial grades should be contaminated. Dawson[4] has listed the impurities which may be found in U. S. P. or B. P. grades of the common cinchona alkaloids. These are shown in Table I, and it will be noticed that the amount of impurity in ordinary quinidine may be quite large.

TABLE I.—POSSIBLE IMPURITIES IN U. S. P. OR B. P. CINCHONA ALKALOIDS.

Quinine*	Up to 2% each of cinchonidine and hydroquinine
Quinidine	6–30% of hydroquinidine
Cinchonine	10%, or even 15% according to Skraup,[1] of cinchonidine
Cinchonidine*	10% of quinine and 8% of hydrocinchonidine

* From the stereochemical point of view it is interesting to note that quinine and cinchonidine appear as impurities with the bases which are believed to have the same stereochemical configuration, that is, with cinchonidine and quinine, respectively.

[1] Skraup, *Ann.*, 197 (1879), 374.

Study of the stereochemical rearrangement of quinine has been in progress in this Laboratory for some time. This reaction, as carried out by Rabe,[5] yields a separable mixture of bases containing quinidine. Rabe gives no account of the properties of quinidine from this source. Since the impurity in the U. S. P. quinine used as starting material is comparatively small in amount, it appeared feasible to prepare pure quinidine by means of this reaction. The preparation was undertaken at the suggestion of Professor W. T. Dawson of the University of Texas.

Preparation of Pure Quinidine.—Several batches of 200 Gm. of quinine were submitted to the action of gently boiling amyl alcoholic potassium hydroxide solution (90 Gm. KOH in 3 L. of amyl alcohol boiling at 127–129°). After removal of quinine from the rearrangement mixture as neutral tartrate, quinidine was isolated as acid tartrate. Ninety Gm. of the crude salt were washed by grinding in a mortar with enough cold water to make a thin paste. This was filtered and the washed salt was dissolved in 600 cc. of hot water. After treatment with

* Contribution from the Department of Research in Pure Chemistry, Mellon Institute of Industrial Research.

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[3] Henry, "Plant Alkaloids," Philadelphia, Blakiston's Son and Company, (1924), page 137.

[4] Dawson, *Internat. Clin.*, Series 40, Vol. 2 (1930), 121. (Reprinted in) *J. Roy. Army Med. Corps*, 56 (1931), 178.

[5] Rabe, *Ann.*, 492 (1932), 242.

a little nuchar, the solution was filtered. The yield of colorless quinidine acid tartrate obtained on cooling the solution was 60 Gm., melting point 130–132°. Fifty Gm. of the recrystallized salt were dissolved in hot water and the base was precipitated with ammonium hydroxide. The ammoniacal liquor was poured off and the product was washed with water. It was dissolved in hot alcohol and the solution was filtered. The free base with alcohol of crystallization separated on cooling in colorless crystals. Anhydrous quinidine of constant melting point 170–171° and rotation $[\alpha]_D$ +262 in alcohol, was obtained on drying over night at 100°. The yield was 25 Gm. Several Gm. more of base were obtained on concentrating the alcoholic mother liquor.

A comparison of the properties of quinidine thus prepared, with those of a sample of U. S. P. quinidine is shown in Table II. Oxidation experiments per-

TABLE II.—ROTATION AND MELTING POINT OF QUINIDINE.

Sample.	Observed Rotation.*	Solvent.	$[\alpha]_D$.	Melting Point.
U. S. P. quinidine	+ 9.92°	Absolute alcohol	+248.0°	162–163° C.
Quinidine from	+10.48°	Absolute alcohol	+262.0°	170–171° C.
Quinine rearrangement	+12.95°	1.8 HCl solution	+323.8°	

* NOTE: The length of tube was 2 dcm. and the concentration 2 Gm. per 100 cc. of solution in each case.

formed on our U. S. P. material by Dr. Alice G. Renfrew, of this Laboratory, indicated that it contained about 20% hydroquinidine.[1] Some data are available in the literature on the rotation of presumably pure alkaloid. Thus Emde[2] reported $[\alpha]_D$ +265° in 97% alcohol on a sample of practically pure quinidine supplied by Amsterdamsche Chininefabrik, Amsterdam, while Lewis and his associates[3] reported $[\alpha]_D$ +323.12° in dilute hydrochloric acid solution, on a sample containing not more than 0.5% impurity prepared by Blagden and Chick in the laboratory of Howard and Sons, Ilford, England. Our data agree well with these figures.

NIGHT BLUE AS AN INDICATOR FOR USE IN VOLUMETRIC TITRATIONS OF ALKALOIDS WITH SILICOTUNGSTIC ACID.

BY H. L. FEINSTEIN* AND E. O. NORTH.[1]

In their study of the use of silicoduodecitungstic acid as a volumetric reagent in the titration of alkaloids, North and Beal (4) used malachite green as an indicator. Malachite green gives a deep bluish green in water, but on the addition of hydrochloric acid the color changes gradually through olive-green, yellow, orange

[1] Hydroquinidine may be estimated by oxidizing at 0° C. with permanganate,[4] whereby quinidine is destroyed and hydroquinidine is unattacked. Allen, "Commercial Organic Analysis," Philadelphia, Blakiston's Son and Co., 5th Edition, Vol. 7 (1929), 466, 490.

[2] *Helv. Chim. Acta*, 15 (1932), 574.

[3] Lewis, Drury, Wedd and Iliescu, *Heart*, 9 (1922), 207.

[4] See reference 4, page 412.

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[1] Associate Professor of Chemistry, University of North Dakota.

and finally, red. In dilute acid solutions, malachite green gives a dark bluish green precipitate with silicotungstic acid, while from the concentrated solutions the red precipitate is formed. However, malachite green has not proved to be entirely satisfactory. The bluish green color, showing an excess of the silicotungstic acid, might be entirely masked by the yellow of the remainder of the unprecipitated indicator; or various shades of green are obtained by the blending of the green and yellow, making it difficult to titrate to the same end-point each time. North and Beal (4) used a concentration of two Gm. of malachite green in 150 cc. of 6 *N* HCl. Other concentrations have been tried; all give fair results after one has become accustomed to that particular indicator.

The present work was undertaken to check and simplify the previous work of Coleman and Beal (2) who tried out 18 triphenyl-methane dyes. They used starch and fibres to concentrate their colors. The method becomes rather cumbersome for routine analysis. Their analyses of the fluidextract of cinchona, in which they left out sawdust-adsorption and clarification, gave higher results than the U. S. P. method.

In view of the difficulty arising from the changes of color from yellow to green when malachite green is used, other dyes which might give a better range were tried. Night blue gives promise of being a good indicator. When night blue is dissolved in hydrochloric or sulphuric acid of moderate concentration, the solution is brown in color. The characteristic blue color of the dye is restored by the addition of water, or by the addition of a small amount of silicotungstic acid. One drop from a solution containing one drop of 0.01 molar silicotungstic acid in 200 cc. of 0.6 *N* HCl will produce a change of color from brown to blue when mixed on a spot plate with a drop of a dilute solution of night blue in acid.

The complete restoration of this color is dependent on the concentration of the indicator. This is a most important point in the use of night blue with silicotungstic acid, since an increase in the amount of night blue present in a drop containing silicotungstic acid will mask the blue color first formed. It thus becomes necessary to choose the concentration of the dye which would give the best results, and also to control accurately the amount of both dye and acid mixed on the spot plate. This was accomplished by a very simple method described here.

EXPERIMENTAL.

I. Preparation of Indicators and Reagents.—Night Blue. Night blue was dissolved in 7–8 normal H_2SO_4 in the concentration of 1.5 mg. of dye per cubic centimeter of solution. The solution must be prepared fresh daily, since decomposition sets in after about 12 hours.

Silicoduodecitungstic Acid, $4H_2O.SiO_2.12WO_3.4H_2O$. This acid was prepared according to the directions of North and Beal (3) and modified by Scroggie (5).

Cinchonine, $C_{19}H_{22}ON_2$, was used to standardize the silicotungstic acid solution.

Quinine Hydrochloride, $C_{20}H_{24}O_2N_2.HCl + 2H_2O$. A U. S. P. sample of quinine hydrochloride was used in titrations with silicotungstic acid.

Strychnine alkaloid, $C_{21}H_{22}O_2N_2$, and *Brucine Sulphate*, $(C_{23}H_{26}O_4N_2)_2.H_2SO_4 + 7H_2O$.

II. Titrations.—A solution of silicotungstic acid approximately 0.01 molar is prepared by dissolving 30 Gm. of the acid in enough water to make a liter of solution. Known amounts of pure cinchonine are dissolved in 5 *N* H_2SO_4 and the solution titrated with the silicotungstic acid solution.

A precipitate first forms with a light colloidal suspension in the supernatant liquid. When the alkaloid is 90% or more precipitated the precipitate becomes flocculent, leaving a clear supernatant liquid. In view of the fact that a mono-alkaloidal salt may be formed and also of the possibility that adsorption by the heavy floc may become excessive, the precipitate is allowed to settle for a half minute or so, and then a drop of the clear supernatant liquid is removed to a spot plate by means of a thick-walled glass tubing having an internal diameter of 1.5 mm. The clear supernatant liquid rises in the glass tubing by capillary attraction to the height of a few centimeters and is then gently blown out on a spot plate. Thus, the size of the drop is controlled accurately. Caley's (1) filtration pipette for spot indicator tests was used during the first part of the investigation but was found to be inadequate. The filter-paper in this pipette is not changed easily, and much time is lost in washing. Also dilution of the filtrate takes place unless the pipette is dried before each trial. The formation of a clear supernatant liquid over a rapidly settling precipitate when the point of neutralization is approached eliminates the need of a special filtering apparatus. The thick-walled capillary tubing serves both as a stirring rod and as a pipette.

A drop of the indicator is then added to the silicotungstic acid on the spot plate by means of a platinum wire loop 2.5 to 3.0 mm. in diameter. The two solutions are then mixed. While the alkaloid is present the color of the drop on the spot plate remains brown. With silicotungstic acid in excess the color becomes blue. The end-point, which is taken at the complete disappearance of the brown color, is sharp and easily reproducible. Using the concentrations and amounts of acid and dye indicated here, the colorimetric end-point coincides with 100.0% precipitation of the cinchonine.

The correctness of the end-point is demonstrated by the fact that filtered portions of the same supernatant liquid now give a slight opalescence with excess of either cinchonine or silicotungstic acid solutions.

The equivalent value of the silicotungstic acid solution in terms of weight of cinchonine per cubic centimeter of acid is thus determined, and the acid solution is then evaluated for quinine, strychnine and brucine. The evaluation of silicotungstic acid solution by evaporation to dryness and ignition is not dependable, since at times free silicic acid or other silicates that were introduced during the synthesis of the silicotungstic acid may be present.

Weighed samples of each of the alkaloids or their salts were titrated with silicotungstic acid using night blue as an indicator, and the recovery calculated. The method of aliquot portions was used to determine the approximate end-point. The method of back-titrating with standard of cinchonine after the end-point is passed can be used but a large excess of the alkaloidal solution must be added and the end-point approached again using only the acid solution. Small amounts of the alkaloidal solution added alternately with the acid disturb the end-point—probably by some adsorption phenomenon.

TABLE I.—VOLUMETRIC TITRATION OF CINCHONINE.

Cinchonine Weighed Out. Gm.	Cinchonine Recovered. Gm.	Per Cent Recovery.
0.0896	0.0895	99.9
0.16835	0.1682	99.9
0.2521	0.2519	99.9
0.0937	0.0937	100.0
0.1426	0.14245	99.9

This titration was undertaken to check the accuracy of the indicator and silicotungstic acid solutions in determining the end-point of the reaction. The accuracy of these titrations is the maximum that can be expected with concentrations of the acid solution used, since the difference between the percentage recovery obtained here and 100% recovery is due to less than $^1/_{20}$ cc. of the acid solution.

1 cc. acid = 0.0057 Gm. cinchonine.

Molecular weight, cinchonine, $C_{19}H_{22}ON_2 = 294.19$.

Molecular weight, cinchonine silicotungstate, $2H_2O.SiO_2.12WO_3.2C_{19}H_{22}ON_2.2H_2O = 3504.9$.

TABLE II.—VOLUMETRIC TITRATION OF QUININE HYDROCHLORIDE.

Quinine Weighed Out. Gm.	Quinine Recovered. Gm.	Per Cent Recovery.
0.0820	0.0824	100.48
0.2152	0.2145	99.7
0.0974	0.0972	99.8
0.0855	0.0856	100.1
0.0621	0.0623	100.3
0.1464	0.1460	99.7

Molecular weight, quinine hydrochloride, $C_{20}H_{24}O_2N_2.HCl + H_2O = 396.70$.

Molecular weight, quinine silicotungstate, $2H_2O.SiO_2.12WO_3.2C_{20}H_{24}O_2N_2 = 3528.9$.

Therefore, 1 cc. acid $= \frac{396.70}{294.19} \times 0.0057 = 0.0077$ Gm. quinine hydrochloride.

TABLE III.—VOLUMETRIC TITRATION OF BRUCINE SULPHATE.

Brucine Weighed Out. Gm.	Brucine Recovered. Gm.	Per Cent Recovery.
0.3092	0.4051	131
0.1257	0.1722	137
0.1181	0.1591	133
0.0529	0.0708	134
0.1627	0.2148	132
0.1474	0.1975	135
0.0823	0.1095	133

Molecular weight, brucine sulphate, $(C_{23}H_{26}O_4N_2)_2.H_2SO_4 + 7H_2O = 1012.64$.

Molecular weight, brucine silicotungstate, $2H_2O.SiO_2.12WO_3.4C_{23}H_{26}O_4N_2 = 4457.9$.

Therefore, 1 cc. acid $= \frac{1012.64}{294.19} \times 0.0057 = 0.01262$ Gm. brucine sulphate.

The accuracy of the recoveries was further rigorously checked by having samples weighed out by one member, and the titrations carried out by the other. The values for the recovery of strychnine and brucine are high but are in substantial agreement with the results of North and Beal (4).

TABLE IV.—VOLUMETRIC TITRATION OF STRYCHNINE SULPHATE.

Strychnine Weighed Out. Gm.	Strychnine Recovered. Gm.	Per Cent Recovery.
0.1381	0.1594	115.4
0.2379	0.2807	118.0
0.0752	0.0879	117.0
0.0832	0.0978	117.6
0.1331	0.1556	116.9
0.1083	0.1268	117.1

Molecular weight, strychnine sulphate, $C_{21}H_{22}O_2N_2 = 334.19$.

Molecular weight, strychnine silicotungstate, $2H_2O.SiO_2.12WO_3.4C_{21}H_{22}O_2N_2 = 4217.5$.

Therefore, 1 cc. acid $= \frac{2 \times 334.19}{294.19} \times 0.0057 = 0.01295$ Gm. strychnine silicotungstate.

SUMMARY.

1. Night blue has been found to serve as an excellent indicator for the silicotungstic titrations of alkaloids.

2. The method developed here is rapid and useful in routine analysis. If the method for the analysis of cinchona bark suggested by North and Beal (4) and modified by Coleman and Beal (2) is accepted as official, the analysis would be simplified by the use of this indicator.

3. The method developed is applicable to the analysis of other amines which form insoluble precipitates with silicotungstic acid.

4. All phases of the discussion presented in this paper are being further investigated.

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GASOMETRIC ANALYSIS OF SODIUM NITRITE IN COATED TABLETS, IN THE PRESENCE OF A BICARBONATE AND NITRATE.*

BY LESTER C. DICK.

Powder a sufficient number of tablets in a mortar, equivalent to about ten grains of sodium nitrite. Extract the powdered material with water until 250 cc. has been collected, testing to make certain that all sodium nitrite has been extracted. This solution will contain the bicarbonate, nitrate and the sodium nitrite.

Twenty-cc. aliquots are used for the determination, transferred to a small beaker and the bicarbonate neutralized with $N/2$ hydrochloric acid using methyl orange as the indicator.

The above solution is carefully transferred to the measuring cup of a Lunge nitrometer and introduced into the measuring tube. Follow this with 5 cc. of dilute

* Scientific Section, A. PH. A., Toronto meeting, 1932.

sulphuric acid and take a reading on the graduated equilibrium tube. Now add exactly 5 cc. of potassium iodide solution and add this to the reading previously taken. As the evolution of gas lessens rotate the measuring tube, being certain to maintain it at a higher level than the equilibrium tube. After the evolution of gas has completely stopped the liquid columns are adjusted to the same level and a reading taken on the equilibrium tube. The above reading minus the reading taken after the addition of the sulphuric acid plus the 5 cc. of potassium iodide solution, gives the cc. of gas evolved.

A blank determination is run by making up a standard solution of sodium nitrite containing 10 grains in 250 cc. of a solution containing approximately the same amounts of the bicarbonate and nitrate as the unknown. This solution is assayed by the foregoing method, the cc. of gas noted and adjusted to normal conditions. The amount of sodium nitrite taken, as represented by the aliquot divided by the cc. of gas evolved, gives the factor for 1 cc. of gas under these conditions.

The following results were obtained by this method:

Solution A—containing in 250 cc., 0.648 Gm. of sodium nitrite, 5 Gm. sodium bicarbonate and 2.0 Gm. potassium nitrate; 20-cc. aliquots representing 0.05184 Gm. of sodium nitrite gave readings of 17.7 cc. of gas and 17.5 cc.

Solution B—containing in 250 cc., 1.296 Gm. of sodium nitrite with the same amounts of the nitrate and bicarbonate as solution A; 10-cc. aliquots of the above solution gave readings of 17.5 and 17.6 cc. of gas.

The average of the readings was taken and the equivalent of 1 cc. was found to be 0.002948 Gm. sodium nitrite at 25° C. and 760 mm.

Tablets containing sodium nitrite, sodium bicarbonate and potassium nitrate were assayed by this method and the following results recorded:

Labeled.	Theoretical $NaNO_2$ Content.	Quantity Determined.	Percentage Found.
1–	0.0324 Gm.	0.0330 Gm.	101.85
2–	0.0324 Gm.	0.03376 Gm.	104.19
3–	0.0324 Gm.	0.03211 Gm.	99.10
4–	0.0324 Gm.	0.03156 Gm.	97.40

CONTROL LABORATORY,
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NEW YORK.

SEPARATION OF ALKALOIDS BY BUFFERS.

Acetic acid plus sodium acetate and ammonia plus ammonium chloride are used as buffers. Harmine and harmaline are separated by first buffer by dissolving one Kg. of the hydrochlorides in 10 kilos water at 80–85° C. Solution is filtered through animal charcoal and treated with three kilos sodium acetate, which precipitates 80% of pure harmine. To separate rest of harmine, operation is repeated on mother liquor. Strychnine is separated from brucine by dissolving one part of mixed salts in 10 parts of 10% ammonium chloride and treating with 10% ammonia water at 80–85° C. until precipitation is complete. Strychnine is filtered and cooled mother liquor is treated for brucine with sodium hydroxide. S. Elgazin, *Khim. Farm. Prom.* (1932), 128–131. Through *Drug and Cosmetic Industry.*

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Strophanthus hispidus may be distinguished from *S. kombé* and *S. gratus* by the presence of calcium oxalate which shows up as strongly anisotropic crystal rosets when cotyledons are examined in polarized light. M. Wagenaar, *Pharm. Weekblad.*, 69 (1932), 1257–1263.

THE PHARMACEUTICAL JOURNALS OF THE UNITED STATES.

A PRELIMINARY REPORT BY MINNIE MEYER.

WITH PREFATORY REMARKS AND AN APPEAL FOR COÖPERATION BY EDWARD KREMERS.

As Miss Meyer points out in the introduction to her thesis[1] this is the fourth attempt at a history of pharmaceutical journalism in the United States. The thesis comprises 179 pages of records, tables and maps. Part I consists of a chronological list of journals that have been published at one time or another, some of which are still being published. Part II is a geographical list, and Part III an alphabetical list of journals. The latter also contains brief accounts of each journal. Part IV consists of tables giving the dates of admission of the several states to the Union, the population of each state according to the 1930 census, the dates of the first drug publication in each state, the total number of journals published at any time in its history and, finally, the number of journals published at present. The tables are supplemented by maps.

Though a fourth attempt, the manuscript makes no attempt at completeness. In order to make the record as complete as possible, the geographical list is herewith published in order that reprints thereof may be sent to representatives of each state for corrections and additions. This seems to be the only practical way, if not the only way, to get at the necessary information. The additional information thus acquired can then be transferred to the other chapters which can thus be made as complete as practicable.

An account of the history of pharmaceutical journalism in all of its phases certainly ought to be worth while and it is hoped that this effort will be supported by those who have knowledge not yet recorded. It may be worth while to state that the thesis as outlined above does not represent all of the information compiled. Thus there is already available an imperfect list covering the periods of issue, *viz.*, weekly, monthly, quarterly, etc. Another list reveals proprietaryship: independent publications, house organs, journals published by pharmaceutical organizations, and those published by educational institutions.

As already pointed out material is also being collected as to the history of each journal. This, naturally, involves a record of the editors as well as an account of the type of journalism pursued by them.

In closing these introductory remarks let me appeal once more to the coöperation of each and every one who reads these lines. If he will but take his own state and send in any supplementary information he or she possesses, the task of each individual will be small, but in the aggregate the results ought to prove worth while.

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Pacific Record of Medicine and Pharmacy, 1886–1886—*Pacific Record of Medicine and Surgery*, 1887–1889.

Pacific Druggist, 1890–1894—*Pacific Druggist and Physician*, 1894–1895.

California Druggist, 1891——.

San Francisco and Pacific Druggist, 1895——.

The Stirring Rod, 1906–1928, consolidated with *California Retail Drug Journal—West Coast Druggist*, 1928——.

Pacific Pharmacist, 1907–1919.

Western Drug Review, 1909——.

Southwest Druggist, 1909——.

Pharmacraft, 1910–1915.

Drug Clerk's Journal, 1910–1920—*American*

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Registered Pharmacist's Journal, 1920–1930, *American Pharmacist*, 1930——.
California Retail Drug Journal, 1915–1928, consolidated with *The Stirring Rod—West Coast Druggist*, 1928——.
Blue and Gold Apothecary, 1932——.

Colorado (1).

Rocky Mountain Druggist, 1888——.

Connecticut (4).

The Prescription, 1891–1897, continuation of *Therapeutic Analyst*, merged into *New England Medical Monthly* and *The Prescription*.
The Drug Reporter, 1895–1895.
Ideas, 1897——.
Apothescope, 1929——.

Florida (1).

Trade Letter, 1927–1929.

Georgia (5).

Southern Drug and Paint Review, 1887–1900.
Southern Druggist, 1901–1908.
Southern Drug Journal, 1902–1906.
Southeastern Drug Journal, 1926——.
Dixie Pharmaceutical Journal, 1926–1928. Combined with *Southeastern Drug Journal*.

Illinois (33).

American Journal of Materia Medica, 1860–1861.
The Pharmacist, 1868–1868—*Pharmacist and Chemical Record*, 1868–1872—*Pharmacist*, 1872–1879—*Pharmacist and Chemist*, 1879–1884, merged into *Western Druggist*.
Deutsche-Amerikanische Pharmaceutische Zeitung, 1875–1875.
Pharmaceutical News, 1878–1879.
The Druggist and Paint and Oil Review, 1879–1880—*Druggist*, 1880–1884. Combined with the *Pharmacist and Chemist* and continued as *Western Druggist*. (See *Western Druggist*.)
Paint, Oil and Chemical Review, 1883——.
Oil, Paint and Drug Review, 1885——.
Western Druggist, 1885–1928, continuation of the combined journals, *The Druggist* and *The Pharmacist and Chemist*. Combined with the *Bulletin of Pharmacy* and published as *Drug Bulletin*, 1928——.
Druggists' Gazette, 1886–1890.
The Druggists' Journal, 1886–1897.
American Drug Clerk's Journal, 1887–1888—*Registered Pharmacist* and *American Drug Clerk's Journal*, 1889–1898.
Peoria Drug Review, 1887–1887.
The Apothecary, 1891–1909.
Druggist's Retrospect, 1891——.
The Graduate, 1893–1895.
Drug Clerk's Journal, 1900——.
Chicago R. D. A. Auxiliary, 1901–1902.
The Organizer, 1902——.
N. A. R. D. Notes, 1902–1913—*N. A. R. D. Journal*, 1913——.
Chicago R. D. A. Notes, 1908–1909—*Chicago R. D. A. News*, 1909——.
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National Drug Clerk, 1913–1921—*Drug Store Merchandizing*, 1921–1922—*National Drug Clerk*, 1922——.
American Medical Trade Journal, 1913——.
Standard Remedies, 1915——.
Chicago Drug Club Messenger, 1915——.
San Talks, 1917——.
The Registered Pharmacist, 1919——.
Journal of the Central States College of Pharmacy, 1919–1919—*Central States Journal of Pharmacy*, 1919——.
Drugdom, 1920——.
Bulletin of the United Medicine Manufacturers of America, 1921——.
Package Medicine Journal, 1923–1925.
Package Remedies, 1925——.
The Illini Pharmacist, 1926——.

Indiana (5).

The Indiana Pharmacist, 1882–1894.
Tile and Till, 1915——.
The Indiana Pharmacist, 1918——.
The Purdue Pharmacist, 1924——.
Purdue News, 1903——.

Iowa (8).

Drug News, 1886——. (Des Moines.)
Drug News, 1902——. (Burlington.)
The Official Register, 1913——.
Armand Broadside, 1920——.
The Bulletin, 1924——.
The Druggists' Mutual, 1924——.
Leo's Non Secret News, 1909–1920.
The Last Word, 1908–1914.

Kansas (3).

Medical Herald, 1867–1870—*Leavenworth Medical Herald* and *Journal of Pharmacy* 1870–1872—*Medical Herald*, 1872–1875.
The Sunflower Druggist's Bulletin, 1916–1927.
Kansas Pharmaceutical Association News Letter, 1927——.

Kentucky (3).

Drug News, 1907–1914.
The Kentucky Druggist, 1912——.
Journal of the Kentucky Pharmaceutical Association, 1926——.

Louisiana (3).

The Southern Pharmacist, 1884——.
The Modern Druggist, 1912——.
Lyon's Latest Drug News.

Maryland (6).

Journal and Transactions of the Maryland College of Pharmacy, 1858–1862.
Drug Market, 1890–1891.
Druggist's Recorder, 1890–1893.
Alumni News Letter, Maryland Coll. of Pharmacy, 1891–1910.
The Pharmaceutical Review, 1892–1893.
The Maryland Pharmacist, 1925——.

Massachusetts (11).

Boston Journal of Chemistry and Pharmacy, 1866–1867—*Boston Journal of Chemistry*, 1867–1880—*Boston Journal of Chemistry* and *Popular Science Review*, 1881–1882—*Popular Science News* and *Boston Journal of Chemistry*, 1883–1893.
Druggists' Advocate, 1870——.
The Laboratory, 1874–1876—*American Laboratory*, 1877–1877.
New England Druggist, 1888–1903—*Apothecary and New England Druggist*, 1903–1904—*Apothecary*, 1904——.
The Spatula, 1894–1925, merged into *Practical Druggist.*
Boston Drug Market, 1896–1900—*Eastern Drug Market*, 1900–1930.
Journal of the Association of the Alumni of the Massachusetts College of Pharmacy, Nov. 1903–June 1905. Sept. 1909–Aug. 1910.
Rexall Review, 1904–1904—*Rexall Advantages*, 1904——.
Purity: A Magazine and Bulletin of Health, Food, Drugs, 1907–1909.
Bulletin of the Massachusetts College of Pharmacy, 1911——.
Patchwork, 1918——.

Michigan (16).

Detroit Review of Medicine and Pharmacy, 1866–1876. United with *Peninsular Journal of Medicine* to form *Detroit Medical Journal*, later *American Lancet.*
Western Medical Advance and Progress in Pharmacy, 1872——.
New Idea, 1879——.
Michigan Drug News, –1884—*American Pharmacist*, 1885–1890.
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Retail Druggist, 1893——.
Pharmacal Notes, 1894–1904.
The Pharmacologist, 1897–1898.
Trio: Therapy, Pharmacy, Biology, 1901–1908.
Modern Pharmacy, 1904——.
The Michigan Druggist, 1908——.
The Journal of the M. S. P. A. and Detroit Retail Druggist's Association, 1912——.
Market Report, 1917——.
Pharmaceutical Error, 1919——.
American Crude Drug Harvesters' Magazine, 1927–1927.

Minnesota (6).

The Northwestern Pharmacist, 1886–1888.
The Drug Store, 1888–1892.
Northwestern Druggist, 1899——.
The Indicator, 1912–1912.
Minnesota Druggist, 1916–1918.
Northwestern Drug News, 1929——.

Mississippi (1).

The Southern Druggist, 1870–1870.

Missouri (12).

St. Louis Drug Market Reporter, 1880–1887—*The Druggist*, 1888–1889—*Meyer Brothers' Druggist*, 1889–1920—*Meyer Druggist*, 1920——.
Drug World, 1881–1883, merged into *Medical Brief.*
St. Louis Druggist, 1882–1887—*National Druggist*, 1888——.
The Western Drug Record, 1884–1925.
St. Louis Drug Intelligence, 1886–1887.
Notes on New Pharmaceutical Products, 1889–1896.
Big Four: Medicine, Pharmacy, Toxicology, Therapy, 1897–1900.
McPike's Bimonthly, 1905–1925.
The Disseminator, 1908–1918.
St. Louis Retail Druggists' Association Monthly Bulletin, 1911——.
The Missouri Druggist, 1917——.
Midwestern Druggist, 1925——.

Nebraska (3).

Omaha Drug and Oil Gazette, 1885–1886.
Western Druggist and Oil Gazette, 1885–1888.
The Omaha Druggist, 1887–1927.

New Jersey (11).

New Jersey Pharmaceutical Record, 1875–1875.
Physicians' Drug News, 1906–1916.
Red Cross Messenger, 1908–1930.
Pharmbote, 1909–1915.
Journal of the College of Pharmacy of Jersey City, 1912——.
Bulletin of the University of the State of New Jersey, 1913–1914—*Bulletin of the College of Jersey City*, 1915——.
Associated Drug News, 1926——.
Consolidated Drug News, 1926——.
℞ *Ray*, 1926——.
New Jersey Journal of Pharmacy, 1928——.
New Jersey Drug News, 1931——.

New York (53).

New York Register of Medicine and Pharmacy, 1850–1851.
New York Journal of Pharmacy, 1852–1854. Forerunner of *Alumni Journal*, see 1894.
American Druggists' Circular and Chemical Gazette, 1857–1866—*Druggists' Circular and Chemical Gazette*, 1867–1906—*Druggists' Circular*, 1907——.
Physician and Pharmaceutist, 1868–1871—*Physician and Pharmacist*, 1871–1879; *Physician and Pharmacist* and the *Bulletin of the Medico-legal Society*, 1879–1879; *Physician and Bulletin of Medico-legal Society*.
Oil, Paint and Drug Reporter, 1871——.
New Remedies, 1871–1874—*American Druggist*, 1884–1893—*American Druggist and Pharmaceutical Record*, 1893–1923—*American Druggist* 1923——.
Humphrey's Paint and Oil Trade and Wholesale Druggist, 1872–1874.
The Druggist, 1873–1875.
Druggist's Advertiser and Trade Journal, 1876–1879.
Oil and Drug News, 1878–1882—*Weekly Drug News and Prices Current*, 1882–1883—*Weekly Drug News and American Pharmacist*, 1883–1885, merged into *Oil, Paint and Drug Reporter*, see 1871.
Formulary and Druggist Magazine, Quarterly, 1879–1896.
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Oil, Paint and Drug Review, 1880–1883.
Deutsch-Amerikanische Apotheker Zeitung, 1880–1918—*Apotheker Zeitung*, 1918——.
Martin's Chemists' and Druggists' Bulletin and Medical Advocate, 1881–1882—*Pharmaceutical Record*, 1883–1893, united with *American Druggist*—*American Druggist and Pharmaceutical Record*, 1893–1923.
An Ephemeris of Materia Medica, Pharmacy, Therapeutics and Collateral Information, Squibbs, 1882–1904.
The American Pharmacist, 1882–1883, consolidated with *Weekly Drug News*—*Prices Current*.
Monitor Medico Farmaceutico, 1883–1883.
The Independent Record, 1883–1885.
The Independent Oil and Drug Journal, 1883–1884—*Independent Journal*, 1884–1887.
Pharmaceutische Rundschau, 1883–1895—*Pharmaceutical Review*, 1895–1909.
The Formulary, Monthly, 1883–1893.
The Pharmaceutical Era, 1887–1932. Published in Michigan from 1887–1894.
Notes on New Remedies, 1888–1911.
Drug Topics, 1889——.
Merck's Monthly Report, 1892–1892—*Merck's Market Report*, 1892–1893—*Merck's Market Report and Pharmaceutical Journal*, 1893–1895—*Merck's Report*, 1896——.
Gaceta Medico-Farmaceutics de Nueva York, 1892–1898.
The Alumni Journal, 1894–1896, continuation of *Annual Report of the Alumni Association of the College of Pharmacy of the City of New York*—*Journal of Pharmacology*, 1897–1904—*Alumni Journal*, 1905–1914—*New York Journal of Pharmacy*, 1914–1915—*C. U. C. P. Alumni Journal*, 1916–1917—*Messenger*, 1924–1931—*New York Journal of Pharmacy*, 1931——.
Monatsblatt des New Yorker Deutschen Apotheker Vereins, 1894–1895.
Monatsblatt, 1895–1897.
The *Buffalo Druggist*, 1895–1897—as *Northern Druggist*, 1897——.
Revista Americana de Farmicia, Medecina of Hospitals, 1895–1921.
Mortar and Pestle, 1895–1896.
Practical Druggist and Pharmaceutical Review, 1897——.
Medico-Pharmaceutical Critic and Guide, 1898–1915—*Critic and Guide*, 1915——.
New York County Medico-Pharmaceutical League Journal, 1899–1901.
The Voice of the Retail Druggist, 1906—*Voice Salesman*.
The Percolator, 1909——.
National Pharmacist, 1912——.
Pharmacal Advance, 1914——.

Weekly Drug Markets, 1914–1916—*Drug and Chemical Markets*, 1916–1926—*Drug Markets*, 1926–1932—*Drug and Cosmetic Industry*, 1932——.
The Spokesman, 1916——.
Drug Trade Weekly, 1918–1922. 1928——. Combined with *Pharmaceutical Era* in December 1922. Breden Publishing Corporation bought publication rights from *Pharmaceutical Era* in December 1928, and continued publication under above title.
Atoms and Molecules, 1919——.
Medicinal Herbs, 1922——.
Squibb Message, 1922——.
Drug Jobbers' Salesman, 1923—*Wholesale Druggist*——.
Drug Trade News, 1925——.
New York Pharmacist, 1927——.
Druggist's Research Bureau, 1928——.
Selling and Service, 1930——.
Bronx Pharmacist.
The Nyalist.

North Carolina (2).

The Dixie Druggist, 1913——.
Carolina Journal of Pharmacy, 1915——.

North Dakota (1).

Papyrus Ebers, 1928——.

Ohio (15).

The Druggist, 1859–1861.
Drug Mill, 1881–1881.
The National Druggists' Journal, 1882–1883.
The Journal, 1884——.
Midland Druggist, 1899–1909—*Midland Druggist and Pharmaceutical Review*, 1909–1926—*Interstate Druggist*, 1927——.
Drugs and Sundries, 1902–1908.
Drug Treatise, 1904——.
Therapeutic Digest, 1905——.
The Ohio Valley Druggists' Association, 1911——.
Merrell Messenger, 1915——.
Goodrich Druggist, 1916——.
The Ohio Druggist, 1925——.
The Reserve Pharmacon, 1927——.
Northern Ohio Druggists' Association.
The Miami Valley Druggist.

Oklahoma (3).

Oklahoma Druggist's Review, 1894–1895.
Oklahoma Druggist, 1894–1926.
Oklahoma Druggist's Bulletin, 1917——.

Oregon (3).

Pacific Drug Review, 1888——.
The Pharmacal Digest, 1895–1898.
The Show Globe, 1911——.

Pennsylvania (21).

Journal of the Philadelphia College of Pharmacy 1825–1834—*American Journal of Pharmacy* 1835——.
Annual Report of the Alumni Association of the Phila. College of Pharmacy, 1865–1891—*Philadelphia College of Pharmacy Alumni Report*, 1891–1893—*Alumni Report*, 1893–1911—*Bulletin of the Philadelphia College of Pharmacy and Alumni Report*, 1911–1921—*Bulletin of the Phila. College of Pharmacy and Science and Alumni Report*, 1921–1925—*Bulletin of the Philadelphia College of Pharmacy and Science*, 1925——.
Drug Printer, 1866–1873.
Druggist's Printer, 1868–1872.
Record of New Remedies and Their Therapeutic Value, 1871–1877.
Philadelphia Druggist and Chemist, 1878–1879—*Monthly Review of Medicine and Pharmacy*, 1879–1882—*Quinologist*, 1883–1884.
The Druggist's Journal, 1882–1889.
The Pharmaceutical Bulletin, 1885–1885.
Philadelphia Drug Oil and Paint Reporter, 1885–1892—*Drugs, Oils and Paints*, 1892——.
The Pittsburgh Druggist, 1887——.
Monthly Retrospect of Medicine and Pharmacy, 1895–1902.
Philadelphia Association Retail Druggists' Bulletin, 1901——.
Western Pennsylvania Retail Druggist, 1901——
Good Fixtures, 1904–1929.
Bulletin of the Philadelphia College of Pharmacy, 1908–1911—*Bulletin of the Philadelphia College of Pharmacy and Alumni Report* (See *Annual Report of the Alumni Association of the Philadelphia College of Pharmacy*, 1865.)
Druco News, 1910——.
Journal of the American Pharmaceutical Association, 1912——.
The Mulford Digest, 1912——.
Women's Organization Nation Association Retail Druggists, 1913——.
The Pennsylvania Pharmacist, 1918——.
Pharmascope, 1928——.

Rhode Island (1).

Claflin's Druggist, 1881–1914.

South Carolina (1).

Southern Journal of Medicine and Pharmacy, 1846–1847—*Charleston Medical Journal and Review.*

South Dakota (1).

The Optimist, 1926——.

Tennessee (6).

The Tennessee Pharmacal Gazette, 1874–1874—*Pharmacal Gazette*, 1874–1875.
The Drugman, 1884–1896.
Southern Journal of Pharmacy and Materia Medica, 1895–1898.
Memphis Druggist, 1915–1929.
Druggist, 1918–1931.
Memphis Retail Druggist, 1928–1931.

Texas (6).

Texas Druggist, 1886–1887—*Texas and Southwestern Druggist*, 1887–1888.
The Southwestern Druggist, 1891–1904.
Fort Worth Drug Reporter, 1887–1889.
The Texas Druggist, 1896–1900.
Southern Pharmaceutical Journal, 1908——.
The International Druggist, 1910–1921.

Virginia (1).

The Virginia Pharmacist, 1916——.

Washington (3).

Pharmaceutical Epitome, 1875——.
Washington State Retail Druggist, 1917–1921—*Western States Druggist*, 1921–1927—*Western States Drug Journal*, 1927.
Moulton's Live Wire.

Wisconsin (12).

Wisconsin Druggist's Exchange, 1892–1902, consolidated with *Northwestern Druggist.*
Pharmaceutical Archives, 1898–1903.
Milwaukee Journal of Pharmacy, 1899–1900.
The Retort, 1900——.
The Wisconsin Druggist, 1903–1909.
The Mask, 1904——.
The Pill, 1910–1920.
Pharmacal News, 1915——.
Journal of the Wisconsin Pharmaceutical Association, 1920–1920—*Wisconsin Pharmaceutical Journal*, 1920——.
The Druggist's Journal, 1923——.
The Badger Pharmacist, 1930–1931.
Drug News.

ASSAY OF AROMATIC SPIRIT OF AMMONIA, U. S. P. X.*

BY J. D. BOOTH.[1]

INTRODUCTION.

Since 1820, and up to the 10th Revision of the U. S. Pharmacopœia, Aromatic Spirit of Ammonia remained without an assay, although specifications of the alcoholic content and the specific gravity were made.

Kebler[2] reports a method for the assay which is as follows:

"Determine the total alkalinity by adding excess acid and titrating with an alkali. In a second sample precipitate the ammonium carbonate as barium carbonate, filter, add excess acid to the filtrate and titrate with an alkali. This titration represents the free ammonia. The difference in the two titrations represents the ammonium carbonate present."

Of the fifty-two samples which he assayed only eighteen per cent came within a ten per cent variation of the standard in the free ammonia content, and even a greater variation in the ammonium carbonate content. Due to the unsatisfactory results obtained, it was thought that by converting the ammonium carbonate to sodium carbonate and ammonium hydroxide that a more accurate assay could be developed.

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* This paper is a development of a thesis presented to the faculty of the Philadelphia College of Pharmacy and Science as a part requirement for a Ph.C. degree, 1930.

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[2] L. F. Kebler, "The Quality of Some Drug Available on the Market and Purchased on Prescription, with Method of Analysis," JOUR. A. PH. A., 6 (1917), 615.

EXPERIMENTAL.

Ammonium Carbonate and Free Ammonia.—Place a 10-cc. sample in an Erlenmeyer flask containing 30 cc. $N/2$ sulphuric acid, boil for three minutes and titrate the residual acid with $N/2$ sodium hydroxide. This represents the total alkalinity (reading A). To another 10-cc. sample, add 30 cc. $N/2$ sodium hydroxide, boil until free from the odor of ammonia, cool and titrate to neutrality with $N/2$ sulphuric acid, using phenolphthalein as an indicator. Note the reading on burette (reading B), add three drops of methyl orange and continue the titration (reading C). Sodium bicarbonate is neutral to phenolphthalein and alkaline to methyl orange; therefore, the difference in the titrations (B) and (C) represents one-half of the carbonate present. Subtract the calculated ammonium carbonate from the total alkalinity, the difference represents the ammonia in a free state.

Alcoholic Content.—Place a 20-cc. sample in a distillation flask, add 5 cc. (1–1) sulphuric acid and 200 cc. distilled water. Distil off 90 cc. and make up to exactly 100 cc. with distilled water. Determine the specific gravity by the use of a pycnometer, and calculate the per cent alcohol. The result represents one-fifth of the alcoholic content of the original solution.

Specific Gravity.—Determine the specific gravity of a new sample by the method given above, or by the use of a Westphal balance.

There being variations in the U. S. P. requirements for ammonia water and ammonium carbonate, several samples were prepared from assayed ingredients to contain the minimum and maximum amounts.

VARIATION IN SAMPLES.

Sample A was prepared on a basis of 30 per cent ammonium carbonate and standard ammonia water. Sample B was prepared on a basis of 32 per cent ammonium carbonate and standard ammonia water. Sample C was prepared on a basis of 31 per cent ammonium carbonate, standard ammonia water, and to contain 68 per cent alcohol in the finished product. Sample D was prepared on a basis of 39 per cent ammonium carbonate, 10.5 per cent ammonia water, and to contain 62 per cent alcohol in the finished product.

RESULTS.

Sample.	Specific Gravity.	Per Cent Free Ammonia.	Per Cent Ammonium Carbonate.	Per Cent Alcohol.
A	0.896	0.370	4.180	62.50
B	0.899	0.330	4.230	61.50
C	0.895	0.360	4.380	68.20
D	0.901	0.390	4.410	62.50

CONCLUSION.

1. Ten samples of each of the various samples prepared were assayed with less than 0.2 per cent variation.

2. The results of this experimental work show that this is an accurate method for the determination of ammonium carbonate and free ammonia in the official Aromatic Spirit of Ammonia.

GIFT OF BOOKS.

A collection of books pertaining to public health, assembled by the late Dr. John S. Fulton, first full time state health officer for Maryland, and executive officer of the state department of health for nearly thirty years, was recently presented to the department's library by Mrs. Fulton. There are more than a hundred volumes in the collection, in addition to pamphlets and charts.

ANIMAL PHARMACEUTICALS OF THE PAST AND PRESENT.*

BY CHARLES WHITEBREAD.[1]

The natural desire which we experience for self-preservation has led mankind, from the earliest ages, to distinguish carefully between those things which minister to health and the prolongation of life, and those which may impair the former and shorten the latter. They have specially directed their efforts to preventive measures, but perceiving that, notwithstanding all their care, they are sometimes taken by surprise and are not able to avoid the causes of injury or disease, they have, as a last resort, devoted their energies to the discovery of remedies and of methods of cure to be applied when precautions have failed.

Seeing that those who died had apparently committed some error which gave to their ailments a fatal character, and that those who survived had made use of certain things, not necessary or desirable in health, to which their recovery was attributable, man was led to avoid the mistakes which proved injurious and to adapt for himself and others the remedies which proved beneficial.[2]

In the progress of civilization various incidents have gradually unfolded the remedial powers of many natural substances. These were recorded and the authentic history of medicine and pharmacy dates its commencement from the period when such records were begun. The Chaldeans and Babylonians, we are told by Herodotus, carried their sick to the public roads and markets that travelers might converse with them, and communicate any remedies which had been used in similar cases. This custom is said to have continued during many ages in Assyria. It is also said that it prevailed among the ancient Lusitanians, or Portuguese. In this fashion the results of experience traveled only by oral tradition.

It was in the temple of Æsculapius in Greece that medical information was first recorded. Diseases and medicines were there registered on durable tablets of marble. The priests and priestesses, who were the guardians of the temple, prepared the remedies and directed their application, and thus commenced the professions of pharmacy and medicine.

With respect to the actual nature of the remedies used by the early Asclepiads it is useless to inquire except in a few instances. The lapse of ages, loss of records, change of language and ambiguity of description have rendered research unsatisfactory. Indeed we are in doubt concerning many of the medicines which even Hippocrates used.

It is shown by the earliest records that the ancients were in possession of many powerful remedies. Thus, Melampus of Argos, a Greek physician who is supposed to have lived about 1380 B.C., is said to have cured one of the Argonauts of sterility by administering for ten days, the rust of iron in wine. The same physician used hellebore as a purge on the daughters of King Praetus who were afflicted with melancholy. Opium, or a preparation of the poppy, was certainly known in the earliest ages.

There are records of ancient magic cures being effected by animal drugs. For instance, a memorial tablet found on the site of an Æsculapian temple records

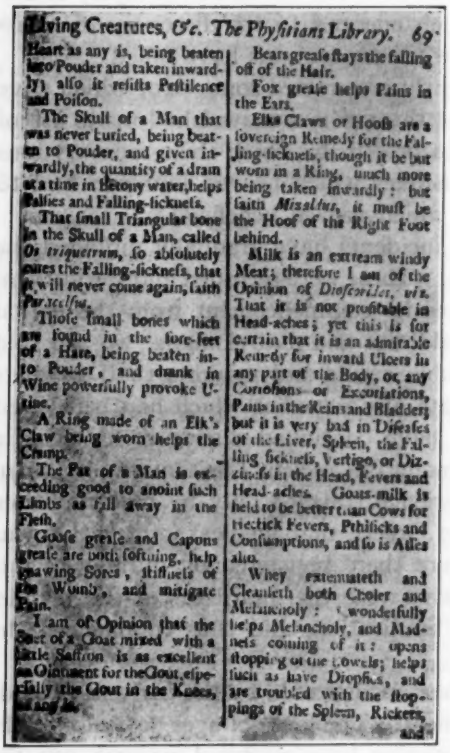
* Section on Historical Pharmacy, A. PH. A., Toronto meeting, 1932.

[1] Assistant Curator, Division of Medicine, U. S. National Museum.

[2] Leclerc, "Histoire de la Medecine."

the following among other cures: "A blind soldier named Valerius Aper, having consulted the oracle, was directed to mix the blood of a white cock with honey, and make of it an ointment which he was to rub on the eyes for three days. He recovered his sight and went to thank the god before all the people."

The endeavor to find medicinal virtues in parts of animals dates back to time immemorial. Mythology furnishes legends of pharmaceutical interest concerning the fabulous animals, the phoenix, the unicorn and the dragon. According to Herodotus the phoenix was a bird about the size of an eagle. It was believed to



Living Creatures, &c. The Physitians Library. 69

Heart as any is, being beaten into Pouder and taken inwardly, also it resists Pestilence and Poison.

The Skull of a Man that was never Buried, being beaten to Pouder, and given inwardly, the quantity of a dram at a time in Betony water, helps Palsies and Falling-sickness.

That small Triangular bone in the Skull of a Man, called *Os triquetrum*, so absolutely cures the Falling-sickness, that it will never come again, saith *Paracelsus*.

Those small bones which are found in the fore-feet of a Hare, being beaten into Pouder, and drank in Wine powerfully provoke Urine.

A Ring made of an Elk's Claw being worn helps the Cramp.

The Fat of a Man is exceeding good to anoint such Limbs as fall away in the Flesh.

Goose grease and Capons grease are both softning, help gnawing Sores, stiffness of the Womb, and mitigate Pain.

I am of Opinion that the Suet of a Goat mixed with a little Saffron is an excellent Ointment for the Gout, especially the Gout in the Knees, and

Bears grease stays the falling off of the Hair.

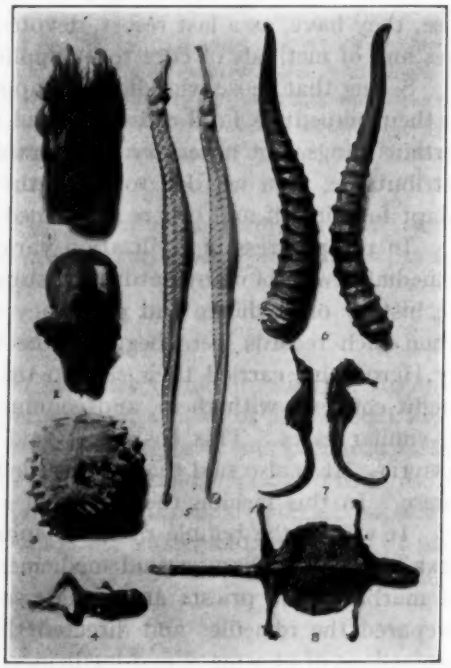
Fox grease helps Pains in the Ears.

Elks Claws or Hoofs are a Soveraign Remedy for the Falling-sickness, though it be but worn in a Ring, much more being taken inwardly: but saith *Mizaldus*, it must be the Hoof of the Right Foot behind.

Milk is an extream windy Meat; therefore I am of the Opinion of *Dioscorides*, viz. That it is not profitable in Head-aches; yet this is for certain that it is an admirable Remedy for inward Ulcers in any part of the Body, or any Corrosions or Excoriations, Pains in the Reins and Bladder; but it is very bad in Diseases of the Liver, Spleen, the Falling sickness, Vertigo, or Dizziness in the Head, Fevers and Head-aches. Goats-milk is held to be better than Cows for Hectick Fevers, Pthilicks and Consumptions, and so is Asses also.

Whey extenuateth and Cleanseth both Choler and Melancholy: wonderfully helps Melancholy, and Madness coming of it: opens stopping of the Bowels; helps such as have Dropsies, and are troubled with the stoppings of the Spleen, Rickets, and

This reproduction (reduced) of a page from Dr. Culpepper's London Dispensatory gives some idea of the forerunners of organotherapy as practiced in England in 1718. —*Courtesy of U. S. National Museum.*



Animal substances as kept in apothecary shops of the past: 1, Bear's claw; 2, charred monkey skull; 3, tortoise shells; 4, dried frog; 5, pipefish; 6, antelope horns; 7, seahorses; 8, lizzard.—*Courtesy of U. S. National Museum.*

be immortal and was worshipped by the Egyptians. It was adopted by the alchemists as their emblem, and was afterward a sign used by the pharmacists. Aristotle described the unicorn as an animal resembling the Indian wild ass, with a single long horn projecting from the center of its forehead. This horn was a medicine, and the unicorn was a frequent sign used by apothecaries. The dragon was associated with pharmacy by means of the "blood" which at one time was supposed to be yielded by it.

Among the animals mentioned in the *Papyrus Ebers* are the buffalo, stag, ox, pig, camel, ram, dog, crocodile, bat, goose, tortoise, beetles and flies. Among

the animal substances used as medicines were blood, human brains, urine, feces, genitals of cats, various animal oils, honey, milk, eggs and wax.

Hippocrates, "The Father of Medicine" (460–370 B.C.), who practiced about 800 years after the period of Æsculapius, the Greek "God of Medicine," mentioned nearly four hundred simples in his numerous writings. These included milks, wines, fruits and vegetables, as well as other substances, which would be classified with the foods of to-day. Among the animal drugs of the time of Hippocrates may be mentioned aparine (goose grease), cantharides, centipedes, crayfish, dog, excrement of the ass, goat, mule, goose and fox, frogs, honey, horns of the ox, goat and stag, ostrich, ox liver, gall and urine, red spider, serpent, sweat, torpedo fish, turtle, wax and worms.

Between Hippocrates and Galen, called "The Father of Pharmacy," an interval of some six hundred years elapsed. Galen was an enthusiastic admirer of Hippocrates, and used all the power of his genius and the influence of his name to maintain the practice of medicine on the foundation laid for it by Hippocrates in the study of the natural history of disease. Galen's writings and teachings had almost undisputed authority in medicine down to the 16th century. It has been estimated that Galen's materia medica consisted of 540 plants, 180 animal and 100 mineral substances. He was a prolific writer on pharmacy, and the preparation of medicines by physical means is still called galenical pharmacy.

It was in the 16th and 17th centuries that the introduction of animal remedies developed rapidly. From the number of animal substances made official in the London Pharmacopœias of 1618, 1650 and 1677, it would seem that the world was ransacked for animal medicines with which to alleviate human ills. Illustrations of apothecary shops of that time usually show a crocodile suspended from the ceiling, and different animal carcasses in other parts of the store. The animal pharmacy of this time, which was practiced in all countries, continued in some parts of the world on an extensive scale till about 50 years ago. It is not practicable to list many of these materia medica specimens, but striking examples of some of those retained in the collections of the United States National Museum and now on exhibition in the Division of Medicine will serve to illustrate this phase of the medicine and pharmacy of bygone days.

Antelope Horns.—The horns of the goat antelope, *Nemorhoedus crispus*. Used, in coarse powder or partially calcined, in cerebral affections and rheumatism, and especially in the various diseases accompanying pregnancy. The shavings, said to be a cooling medicine, were supposed to cure inflammation of the lungs and liver.

Bear's Gall.—The gall-bladder of a bear was valued as an alterative, anthelmintic and nerve stimulant, and was used especially in hepatic and other abdominal diseases.

Bear's Paw.—The skin of the foot, with the nails, of a species of bear. The bear's paw was considered a great delicacy, and was supposed to strengthen the constitution.

Bird's Nest.—The gelatinous nests of several species of the swallow, *Collalia esculenta* and others, were regarded as a valued and expensive article of food, and was accounted a tonic and invigorating remedy for the sick.

Caterpillar.—The dried larvæ was used in bronchial complaints and as a purgative and antispasmodic.

Centipede.—The head and feet being rejected, the rest of the dried animal was reduced to powder. It was given for demoniacal possession, malarial fevers, obstruction of the bowels, for worms and for snake bites.

Cicada Skins.—The exuviæ of a species of *Cicada*, or locust, was used for difficulties in

speech; for dimness of vision and cataract; for bringing out the eruption of smallpox, and for convulsions and other diseases of children.

Clam Shells.—The powdered shells were used for colds, chills and fevers, and as a cathartic.

Cockle Shells.—The powdered shells of a bivalve mollusk were given for chills, and for intestinal obstruction.

Coral.—In fine powder it was used to arrest hemorrhage from the nose and to remove nasal polypi. It was also applied to opacities of the cornea.

Cow Bezoar.—A concretion (biliary calculus) found in the gall-bladder of the cow was a remedy for chorea, smallpox, insanity, apoplexy and palsy. It was given to newborn infants as a charm and prophylactic.

Cuttlefish Bone.—The internal shell of a species of *Sepia*. Said to be styptic, alterative and anthelmintic. In powder it was used locally to arrest hemorrhage, and internally for cancer.

Deer's Horn.—Hartshorn was formerly an expensive medicine, and all sorts of therapeutic properties were attributed to it.

Dragon's Bones.—Fossil bones of the *Stegadon orientalis*, reduced to a fine powder. Used in ague, fevers, hemorrhages and fluxes.

Dragon's Teeth.—The fossil teeth of various animals were known by the name of dragon's teeth. They were supposed to act on the liver, and to be of service as cordial and sedative remedies.

Dried Frogs.—The common frog dried without removing the skin or viscera. Soups and gelatin prepared from these animals were thought to be especially strengthening for convalescents.

Dried Mussels.—The common salt water mussel dried. Claimed to be aphrodisiac; also a remedy for post-partum hemorrhage, for colic and intestinal obstruction.

Dried Toads.—Skinned, eviscerated and dried. They were said to be tonic and sudorific.

Dung Beetle.—Gathered on the fifth day of the fifth moon, the feet and elytra discarded, and the insect roasted or boiled. Used for chills and fever, convulsions and insanity.

Earthworms.—They were reduced to powder and used as an anthelmintic; for fever, jaundice, ulcerated throat, snake and insect bites.

Elephant's Hide.—A small piece of the skin of an elephant entered into the composition of certain plasters used for the cure of contusions.

Fossil Crab.—In powder it was applied to ulcers, wounds and snake bites; mixed with wine or oil it was given for chronic dysentery and pernicious fevers.

Fossil Shells.—Undetermined species of fossil shells belonging to the genera *Spirifer* and *Rynchonella*. Held in the hands of parturient women they were said to facilitate delivery. Powdered they were applied to opacities of the cornea and to the eruptions of scabies; internally they were given for diarrhoea and hemorroids.

Fowl's Gizzard.—The lining membrane from the gizzard of the common domestic fowl was prescribed in dyspepsia, diarrhoea and urinary disorders.

Goat's Blood.—The dried blood of the mountain goat. It was used as an application to bruises, and as a remedy for amenorrhoea and certain conditions following childbirth.

Haliotus Shells.—The shells of *Haliotus funebris*, a bivalve mollusk. The outer layers were removed and the pearly portion reduced to fine powder, which was applied to opacities of the cornea and to the films of pterygium. It was also a remedy for diseases of the liver.

Hedgehog Skin.—The skin of the head of the hedgehog. A decoction of the skin was used for pulmonary complaints; powdered and made into pills it was taken for the cure of skin diseases.

Human Feces.—Mixed with a large proportion of vegetable fibre, this was used as a remedy for hydrophobia, and as an antidote for certain poisons.

Human Hair.—Human hair was reduced to charcoal by burning in a closed vessel and was given as a remedy for hematemesis.

Human Placenta.—The dried human placenta was considered a tonic in consumption. Roasted, it was given, in the form of pills, to parturient women to facilitate the expulsion of the fetus.

Human Urine.—The urine of children, to which common salt or calcium sulphate had been added, evaporated to dryness. It was given in debility, and in renal, vesical and uterine complaints. It was also used as a lotion for sore eyes.

Inner Membrane of Eggshell.—The dried membrane lining the inner surface of fowl's eggs was used as a plaster to close small wounds.

Ivory.—Supposed to be taken from a living elephant. The powder was believed to be stomachic, vulnery and diuretic, and the jelly was a specific for rickets.

Larvæ of Flies.—The dried maggots of blue bottle and house flies. They were given as a remedy to cachectic and scrofulous children.

Maggots.—The dried larvæ of a species of *Eristalis*. Prescribed in the delirium of fevers and for dysentery.

Mole Cricket.—The anterior portion of the insect was used for polyuria and diarrhoea; the posterior portion for retention of urine and constipation. It was also used for difficult labor, hiccough and bad ulcers.

Monkey's Skull.—Animals, or parts of animals, were enclosed in coarse clay vessels and subjected to heat until thoroughly carbonized. Thus prepared they were kept in shops and sold for medicinal purposes.

Musk.—The sac, containing musk, taken from the abdomen of the musk deer, *Moschus moschiferus*, was believed to purify the air, cure melancholy and protect from the bites of serpents.

Ox Gall.—The dried gall-bladder of the ox, with its biliary contents, was said to be tonic, stomachic and laxative, and was used in the treatment of diseases of the digestive organs.

Oyster Shells.—The partially calcined shells of the oyster. They were said to be tranquilizing by nature, and in powder were used in malarial fever and various diseases accompanied by hypersecretion.

Pangolin Scales.—The scales from the body of *Manis javanica*, scaly ant eater. Formerly used in all sorts of diseases, especially of the skin.

Rhinocerus Horn.—Tonic, alterative and other properties were attributed to these horns. The decoction was taken in fever, smallpox, hemoptysis.

Scorpions.—Roasted and powdered this medicine was used for all forms of paralysis, for small-pox, scrofula, convulsions and abdominal tumors.

Sea Horses.—Used as a stimulant; also had the reputation of facilitating parturition; it was sufficient that the patient hold one in her hand.

Seed Pearls.—Powdered and given internally for diseases of the heart and liver; externally applied to ulcers and opacities of the cornea, to the auditory meatus for deafness, and to the pustules of smallpox.

Silk Cocoons.—They were burned, the ashes mixed with wine and taken internally in order to cause the bursting of abscesses.

Silkworms.—Washed in rice water, boiled in a decoction of ginger, and dried they were used for convulsions in children, for menorrhagia and as an aphrodisiac.

Silkworm Moths.—Roasted moths. This medicine was thought to be aphrodisiac and a remedy for impotence.

Snails.—The common garden snail collected in the 5th month. They were used for lameness, rectal prolapse, convulsions, retention of urine, etc.

Snake.—Believed to be a useful remedy for abdominal pains. From its habit of hiding in hedges and crevices it was supposed that, mixed with other drugs, it aids them in penetrating the most secret recesses of the body.

Sparrow Dung.—The excrement of the common house-sparrow, mixed with powdered peppercorns and made into a mass with alcohol, was applied to the skin to produce local anesthesia preliminary to the opening of abscesses or extraction of foreign bodies from wounds.

Spiders.—Used for fever sores, boils, and to neutralize the poison of snakes and venomous insects.

Tortoise Shell.—Jelly made from the plastron, or the powdered shell made into pills or mixed up in cakes, was reported to be tonic, cordial, astringent and useful in diseases of the kidneys. The ashes were given to parturient women and dusted upon wounds and ulcers.

The method of reasoning of the middle ages—pure deductive reasoning from accepted premises—formed the basis of the old systems of medication. From some general hypothesis, accepted without proof and believed to represent a truth

of universal application, deductions were made about all diseases and all remedies. For example—to cite only the selection of medicines by the doctrine of signatures—it was believed that the Creator in providing plants and other objects for the service of man had stamped on them, at least in many instances, an unmistakable sign of their special remedial value. Many of the animal remedies listed were probably chosen by some imaginary relation between the characteristics of the medicinal material and the symptoms of the disease. Thus, cicada skins might have been selected as a remedy for difficulties in speech because this insect had the power of producing such a shrill and prolonged sound, and parts of snakes were used for the reason that it was thought this reptile could "penetrate the most secret recesses of the body" as it did crevices and hedges, and thus carry the remedy mixed with it to the seat of the trouble.

Francis Bacon upset the deductive sort of reasoning completely as a method of arriving at the truth in the material world, and to-day observation of facts, explanation of relations between facts, establishment of rational general principles, and scientific interpretation form the basis of our reasoning in applying and extending knowledge in the sciences. Under Bacon's system animal remedies were put to the test, and health-restoring and life-saving specifics came into use.

The animal kingdom's contributions to materia medica now became important. Jenner's vaccination of James Phipps on May 14, 1796, with cowpox virus from the arm of Sarah Nelmes furnished an animal remedy with the power to prevent smallpox, one of the world's greatest scourges, which, it is estimated, in every twenty-five years deprived at least 15,000,000 human beings of life, and left millions disfigured, weakened, crippled and sightless. We have learned that only one agent can keep smallpox in check, and that is vaccination. We know, too, that this animal remedy has done its work so well that a dreadful scourge is almost forgotten.

Charles Edouard Brown-Sequard, at the age of seventy-two at a meeting of the Paris Societe de Biologie in 1889, described the now famous experiments he had performed upon himself by the subcutaneous injection of testicular extracts which resulted in increased physical strength, improved appetite, regulation of bowel function and increase of mental activity. His report stimulated research in internal secretions, and resulted in the development of organotherapy, and its firm establishment in the treatment of disease. Thyroid, pituitary and epinephrine are now included in our pharmacopœia, while ovary, corpus luteum, mammary and numerous other organotherapeutic products are used all over the world in fields in which they are practically alone.

Emil von Behring, working in Koch's Institute with Shibamiro Kitasato, demonstrated that the serum of animals immunized against attenuated diphtheria toxins could be used as a preventive or therapeutic inoculation against diphtheria in other animals, through a specific neutralization of the disease. After trying out the remedy in man, Behring began to produce it on a large scale in 1894, and it soon became recognized as the specific treatment for diphtheria.

No more striking example of North American research along this line can be given than the evolution of insulin by Banting and Best in 1922. This glycolytic extract with its power of increasing the metabolism of sugar is daily prolonging the activity and usefulness of persons afflicted with *diabetes mellitis*.

And now animal remedies have come into their own to such an extent that we cannot think of the most modern and successful of our medicinal agents without thinking of serums, vaccines and organotherapeutic products in general. In fact, there is perhaps no better way of demonstrating the upward progress of medicine and pharmacy than by comparing the make-shift animal remedies of the past with the scientifically proven ones of the present.

PIONEERS IN AMERICAN PHARMACY.*

Among the first of the pioneers in manufacturing pharmacy may be mentioned Dr. Edward R. Squibb. This talented physician-pharmacist in his attempt to reconcile discordant conditions in the ethics of medicine and those of pharmacy as applied to business in the early annals of American pharmaceutical evolution, met with disappointments and resistances from various interested parties. But in it all he established a reputation for unquestionable service.

His introduction to the pharmaceutical world was as Assistant Director of the Government Laboratory, New York City, 1855. When came the fire that destroyed his modest pharmaceutical establishment, scattered his moderate fortune and burned him so badly as to nearly destroy his life, undiscouraged by it all, on his recovery he turned his face to the future. With the help of admiring professional friends and the influence of a host of confiding pharmacists, he built for himself a new establishment, in the conduct of which he endeavored to unite and affiliate the scientific, professional and commercial, in medicine and pharmacy. He thus established his name imperishably in the annals of American pharmacy. For many years the house of Edward R. Squibb and Company has enjoyed the unqualified confidence of American physicians and apothecaries. To-day it is immeasurably greater than its founder could even have anticipated.

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As a co-laborer in America's early records, especially connected with the American materia medica, the founder of the William S. Merrell Chemical Company, rises to view. Well does this writer remember him. Modest and unassuming, cordial to every one, Mr. Merrell was most earnest in his efforts, the beginnings of which were in a circumscribed retail pharmacy that occupied a small corner room in the building where these lines are now being written.[1] Closely associated in companionship with William S. Merrell was Dr. T. L. A. Greve, his able clerk assistant, whom no incentive could lure from prescription life. To these two

*At the meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION, Put-in-Bay, 1899, a prominent member asked me to write an article on the subject embraced by this paper. I replied that in my opinion it was not yet time to make the record of the past. But while the subject was on my mind, on my return to Cincinnati, I wrote offhand the record as I knew it. That paper was resurrected by my son, John Thomas Lloyd, who gave it to Editor Eberle for publication if he desired. In reading it the date at which it was written must be kept in mind.

[1] His son George succeeded to the business, which in turn his children have inherited and furthered. Many honors have come to them. Charles Merrell, whom this writer takes pride in counting as one of his friends, is now the chief and very active guider of the firm of Wm. S. Merrell Company.—J. U. L., 1933.

pioneers, concerned in American plant pharmacy, we owe a debt of gratitude—William S. Merrell, the genial charming manufacturer, Dr. Greve, the exceptionally gifted scientist-apothecary.

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Co-laboring pioneers in the American field of plant pharmacy were the Tildens of New Lebanon, N. Y. (H. A. Tilden, founder), who conducted the first great eastern laboratory devoted mainly to medicinal plant preparations. In connection therewith was established perhaps the most extensive of all American medicinal-plant gardens. In the Tilden laboratory was first established and applied vacuum apparatus devoted to medicinal plant manipulations on a large scale. Working with the Tildens were the Shakers of Lebanon, N. Y. Hand in hand they worked, their efforts contributing to the opportunities and progress of the great Tilden establishment, described editorially by Prof. William Procter, Jr., in the *American Journal of Pharmacy* (1855), as a wonderful sphere of pharmaceutical activity.

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Contemporary with the Tildens we find Frederick Stearns of Detroit, one of the most enthusiastic contributors to botanical medicinal literature connected with early American pharmacy. His treatise on the *Medicinal Plants of Michigan* stands to-day as authority in the records of the AMERICAN PHARMACEUTICAL ASSOCIATION, to which organization his early contributions were voluminous and exceptionally useful. The establishment founded by him, Frederick Stearns & Company, covers one of the choice squares of Detroit, and stands as a tribute alike to the foresight of the founder and the energy of his successors.

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Well do I recall when, after the close of the Civil War, Colonel Eli Lilly came from Lexington, Ky., to the young and growing city of Indianapolis, to engage with Johnson in drug-mill pharmaceutical efforts, from which—after separation of the partners, grew the world-renowned establishment of Eli Lilly and Company. The founder of this establishment was not in affluent circumstances. He prepared with his own hands the preparations bearing his label, bottled and packed the compounds, marked and shipped them personally, content and happy in the opportunity of so doing. I believe that all will now agree that the name of this family stands second to none in pharmaceutical activity.[1] To me the friendship with the founder of this establishment is one of my cherished recollections.

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Next uprises the face of Mr. Parke, of Detroit, who established what was destined to become the world-renowned house of Parke, Davis & Company. To one of the first Cincinnati Expositions, he brought from Detroit, a modest assortment of pharmaceutical preparations, and himself attended to setting up and caring for the display. Soon thereafter came into the business, first as a traveling representative, next as a partner, George S. Davis, who united with the efforts of Mr. Parke his most remarkable business management. The most conspicuous and aggressive was he of all men to that date concerned in the manu-

[1] After the founder came his son, J. K. Lilly, under whose guidance the establishment advanced with marvelous strides, and now (1933) the grandsons of Eli Lilly are carrying forward this great institution.

facture of American pharmaceutical preparations. Indeed, in this writer's opinion, the systematic processes of George S. Davis instituted a new phase in the then developing pharmaceutical business processes of all American manufacturers. A phenomenal man was he, whose innovations in manufacturing pharmacy marked an epoch in American pharmacy that this writer believes should be, and will be, conceded by every one. The scholarly Professor Ryan and his corps of able co-laborers, on whose shoulders has fallen the responsibility of the great Parke, Davis establishment, surely recognize that this tribute is not overdrawn.

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Come now to view the faces of "Charlie and Louis" Dohme, of the well-known pharmaceutical establishment in Baltimore. No one could have foreseen when I first visited the retail apothecary shop of Sharp & Dohme, that within a very moderate period as history counts time, preparations bearing their label would be in every pharmacy in America. No fairer business men ever lived, no more charming companions, than "the Dohmes," which applies also to A. R. L. Dohme,[1] son of Charles, who now conducts the establishment, and is so fortunate in his exceptionally systematic scientific education.

In this connection one cannot neglect to mention the name of Charles Caspari, the energetic co-laborer with and advisor of the Dohmes, to whom the side of professional pharmacy, heired from his no less talented father, appealed, rather than did manufacturing expansion. Scientific was he to the extreme. His son, Charles Edward Caspari, now devotes his efforts to the interests of the well-known establishment of the Middle West, Mallinckrodt and Company of St. Louis, where to a high degree he maintains the reputation of his forebears.

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Possibly no manufacturing pharmacist of the early days in the Middle West was more endeared to his circle of physician friends than was Harlow M. Merrell, nephew of William S. Merrell, with whom he was first associated, being his successor in the Court and Plum Street business location in Cincinnati. Indifferent to the business phases that appealed to many others, Harlow did well his work as an apothecary, expanding therefrom into a specialty business, embracing the manufacture of preparations derived chiefly from America's medicinal plants. In my recollection no man concerned in pharmacy had a more delightful personality than the affable, cultured and unconventional Harlow M. Merrell, the early partner of the writer of these lines. The establishment, much expanded, still stands on the old corner which has been occupied as a pharmacy since 1845.

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Phenomenal was the record of the brothers, W. J. M. and O. F. Gordon, in Cincinnati. Coming from Baltimore in the early part of the nineteenth century, they established a small apothecary shop on the corner of Western Row (now Central Avenue) and Eighth Street. Expanding into a physicians' supply house but yet retaining an increasing prescription business, they ultimately became wholesale druggists as well as dispensing pharmacists. Situated near the old Eclectic Medical Institute, they naturally made a specialty of America's botanicals.

[1] In later years, I believe he has not been active except as an executive director.—J. U. L., 1933.

Neighbor to Procter & Gamble, who then ran their "sweet water" into the canal as a waste product, Gordon saw his opportunity, caught the "sweet water" daily in a box wagon and began the manufacture of glycerine. A large factory became necessary, but it was not until years later that Procter & Gamble and other Cincinnati soap manufacturers comprehended their opportunities in this direction. The Gordon brothers were not only active business men but were excellent citizens of decidedly attractive personality, as this writer who was then apprenticed to them can attest.

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No article concerning early American pharmaceutical activities on a large scale would be complete without the name of George J. Seabury, veteran maker of medicinal plasters, of the firm of Seabury and Johnson. Of all the membership of the AMERICAN PHARMACEUTICAL ASSOCIATION, Seabury was the most cosmopolitan "mixer." No meeting of the ASSOCIATION was considered complete without the presence of the versatile George Seabury. At these meetings he was always accompanied by his two daughters, whom every one admired from their very childhood. In many respects very like George S. Davis, Seabury possessed one decided advantage. Davis seldom took any personal part in pharmacists' gatherings, while Seabury was always in evidence, making many friends, as well as a few antagonists. He took an active part in New York City politics, was an expert fisherman, writing a series of verses on the Black Bass which were illustrated, privately printed and presented to his circle of friends.

Came finally the re-arrangement of the firm of Seabury and Johnson, the Johnson Brothers retiring from the business to found the firm of Johnson and Johnson, while the time-honored name of the old firm was retained by Mr. Seabury. Johnson and Johnson were not long in establishing their reputation as manufacturers of sanitary products, such as absorbent cotton and medicated plasters of the highest quality.[1]

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Before sugar-coated pills were made in America, at least before they were offered to the trade (so far as I am informed) there came from France a line of cumbersome sugar-coated products, labeled "Dragees." These were oval, nearly as large as the first joint of the little finger, sugar-coated, reminding me of the confection known as sugared almonds. They helped to make an opportunity in which Wm. R. Warner, an apothecary of Philadelphia took the initiative. Within a short time Warner's sugar-coated pills were a standard and soon found in every drug store in America. However, the monopoly did not long continue. Candy makers everywhere were expert sugar-coaters, their pharmacy needed little other apparatus. In this writer's opinion, Mr. Warner, by his energy at the very start, founded a national business that expanded far beyond his anticipations. Many

[1] F. B. Kilmer was an apothecary-apprentice, who passed successively from errand boy and clerk in a small pharmacy to the management of this, one of the greatest manufacturing, pharmaceutical establishments of America—probably the largest of its kind in the world. Kilmer soon became at home in every department of the huge establishment, from the chemical laboratory to the distribution of the products. He is generous, self-sacrificing, a delightful companion, a student of historical pharmacy—one whose friendship I greatly cherish.—J. U. L., 1933.

pleasant visits have I had with Mr. Warner at the meetings of the AMERICAN PHARMACEUTICAL ASSOCIATION.

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Almost simultaneously came the American Elixir crusade, the pioneer specimen being introduced under the label, "Sim's Cordial Elixir of Calisaya," 1839. This was an aromatized cordial, conspicuous for its lack of the bitterness of Calisaya. It opened the "elixir" door, special advantage of the opportunity being taken by the firm, John Wyeth & Co. of Philadelphia. The energetic manner in which their preparations were advertised and distributed, made "Wyeth's Elixirs" as well known as were the Fluidextracts of Burroughs Brothers and Thayer, the Pharmaceutical Preparations and Chemical Apparatus of Bullock & Crenshaw, Philadelphia, the Pressed Herbs of B. O. and G. C. Wilson of Boston, or the Resinoids and Concentrations of Keith.

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Among the wisest of pharmacists occurs the name of C. B. Allaire, of Peoria, Illinois. Wise, because when came the opportunity, before he was confronted with age or weighted with an overgrown business, Mr. Allaire sold his interest in the thriving establishment of Allaire, Woodward and Company, and retired to a life of serviceable ease in San Antonio, New Mexico. There his mental activity was stimulated by helpful literature and intelligently applied efforts in economic research and its practical application. The establishment he founded and so ably guided to success, at an early date made a specialty of botanic drugs, both pressed and powdered, maintaining a leadership therein, as well as in general pharmaceutical directions.

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The name of another man living to-day comes now to mind, Professor Edgar L. Patch, of Boston. A professional pharmacist was he, a teacher in the Boston College of Pharmacy. As a partner in the firm of prescription apothecaries, Canning and Patch, he has disproved the often-made assertion that a professional man is not a business man. The preparations of the expanding Patch establishment stand second to none, and the confidence of all who know him is extended to the founder.[1]

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This fragmentary record cannot be made complete—the subject is expanding hopelessly as these words are penned under recollection's touch. The aim is merely to present the names of a sufficient number of our American pharmaceutical manufacturing establishments to use as an object lesson—not to make a complete record either in number or detail of activities. Many essential features must be neglected in directions that will appeal to others. However, enough has been said for the purpose of this paper. Whoever studies it must be indeed a pronounced cynic or a pessimist if (accepting that one feature of importance is success in business) he asserts that pharmacy of the recent American past, as well as of the active present, offered no expansive business recognition to its devotees. Not only has the reverse proved true in the efforts of those mentioned but of numbers unmentioned.—JOHN URI LLOYD.

[1] Professor Edgar L. Patch passed away in 1924.

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

TEACHING LABORATORY WORK IN PHARMACY.*

JESSIE I. MACKNIGHT.[1]

"The following paper by our Canadian confrère, Jessie I. MacKnight, clearly sets forth the fact that teaching problems know no country and that the difficulties met by the American teachers are almost identical with those met by teachers in other nations. The American Association of Colleges of Pharmacy welcomes the following contribution by Miss MacKnight. The sane treatment of the subject of "Teaching Laboratory Work in Pharmacy" will appeal to all."—C. B. JORDAN, *Editor.*

Pharmaceutical laboratory work appears to fall into two sections, practical pharmacy and practical dispensing. The former includes the compounding of all B. P., U. S. P., N. F. or other formulas and work along such lines as suitability of coloring or flavoring agents, tests for purity or solubility of drugs and in compatibility in all its phases. In such a class the work is outlined for the student and he is expected to look up his data, work out his formulas, check up his results and write out a systematic report of all work done. The instructor is at all times available for direction or for consultation and from time to time lectures are given on the more important phases of the work. The class, as time goes on, evolves itself into one of research. The student learns where to look for data, how to apply it when found and gradually develops his ability to think, to reason and to be self reliant and efficient.

A druggist sends in the request—"Can you give me any information on the following difficulty? An emulsion of cod liver oil containing syrup of ferrous iodide turns brown on standing a short time. With some grades of oil this appears to be more pronounced than with others. Is this color change due to the oil or how may it be accounted for or prevented?"

Another friend of the college sends a sample of a powder with the statement that several barrels were bought at a sale of ship's cargo—what is it? Still another makes a request for a suitable coloring agent for a polish—sample submitted. Such requests together with problems that arise in class are turned over to the senior students of the practical pharmacy class and though their findings may not be conclusive they derive much benefit from attempting to solve the difficulties, the fact that the problems are not theoretical adding incentive to accuracy of detail.

A practical dispensing class is conducted along very different lines.

Elementary classes especially are under the close supervision of the instructor. At this stage neatness, quietness, accuracy and ordinary technique are stressed, the main object being to inculcate correct habits in manipulation and procedure rather than to develop initiative. Only simple prescriptions are dispensed and the student is required to follow a given procedure. In senior classes manipulation is

* Delivered before the Teachers' Conference on Pharmacy.

[1] Lecturer and Demonstrator in Dispensing, Maritime College of Pharmacy, Dalhousie University, Halifax, Nova Scotia.

further developed and the student not only carries on more advanced prescription work but adds to this the solution of problems which arise. He is now encouraged to use his initiative. He deals with prescriptions in all their varied forms from the simplest mixture or powder down through the whole line of emulsions, ointments, suppositories, pills, troches, tablet triturates, konseals, ampuls and all types of sterile solutions and has many opportunities to put into practice the fund of knowledge he has acquired or is acquiring in his Materia Medica, Chemistry, Practical Pharmacy or other classes.

He has by this time sufficient knowledge of chemistry to enable him to discuss intelligently the subject of incompatibility; he has also done a considerable amount of investigative work in his practical pharmacy classes and is in a position to apply this knowledge to his prescription work; methods of overcoming or of preventing incompatibility have been devised, unusual prescriptions have been discussed and dispensed. All of this rounds out his course and forms the background for future work in experimental dispensing.

In the modern dispensing class there are at least three types of students to be considered—those who are preparing to enter retail pharmacy, those who intend to practice as hospital pharmacists and to whom dispensing is a main issue, those who will proceed to Degree work and thence to other professional branches such as teaching or research. A course must be outlined which will meet the requirements of all and should be systematically built up.

When the student has learned how to prepare drugs to be used as ingredients in powders, he is then able to apply this knowledge to the preparation of ingredients for ointments. This normally carries him to mixtures, where solubility is added to his knowledge, also types and choice of vehicles and compatibility.

In emulsions he is taught the preferable method to use in the case of fixed and volatile oils. Here also he gains a knowledge of saponification and its application to external and internal preparations.

In pill making he studies types of pill masses whether organic or inorganic, and the excipient or coating best adapted to each case.

He makes konseals by machine and by hand, tablet triturates with their minuteness and potency of dosage, also lozenges in diversity of type and of basis.

Suppository making is a good test of technique. The student is taught to make hand-made molds from wax paper, parchment or plaster of Paris, for use when the heat process is involved. Thus, though he occasionally employs them, he is never dependent on metal molds which are often not suitable in size or in kind. The several types of suppository machines are demonstrated and used. Hand manipulation is perfected so that he may not think the making of a batch of suppositories an irksome task.

The preparation of ampuls and many types of solutions for sterile injection such as intravenous and intramuscular solutions, also sterile saline and sterile oils, is gone into very thoroughly. This may be made one of the most interesting and fascinating parts of the course. Ample practice is allowed in several methods of sterilization such as by the Arnold sterilizer, by autoclaving and by simple boiling. The making of ampuls extemporaneously from test-tubes, specially prepared, is another interesting phase of this work. The lecture periods preceding such laboratory classes would include discussion of glass, its general suitability for ampuls and

tests for its neutrality and solubility, also methods of filling, sealing and sterilizing the ampuls.

What is the relation of lecture work to such laboratory classes?

In the practical pharmacy class, lectures are largely displaced by the student's own research. The instructor uses the time assigned to discuss the work in progress and to compare results so that the lecture period follows the laboratory period. On the other hand the lectures of the dispensing class deal in advance with the work of the day or of the week.

When the student of the latter class fully understands his subject and the principles he is about to apply, he then only requires sufficient repetition, under supervision, to become skilful in turning out his products with speed and dexterity. If pill making is to be taken up in the laboratory, the preceding lectures will not only include discussion of the characteristics of drugs commonly administered in this form but will also include the necessary information regarding excipients and preservatives. Pill coating will include instruction in gelatin coating with or without coloring, silver coating, and pearl coating, also shellac, salol, formalin and other enteric coatings. Pill making and coating is practiced until the student becomes proficient in recognizing types and in turning out creditable products.

A dispensing class at its best correlates the lecture work with the practical. A course which stresses memory work and in which the student follows set rules, depending largely on memory for his technique, does not produce the results for which our colleges of Pharmacy aim. If he has only assembled a mass of facts and rules our graduate falls far short of the ideal. If on the other hand he has acquired the ability to use his knowledge, has learned how to locate and to use additional data, how to reason through rather than to follow blindly or to lean upon his text-books; if he has developed the ability to coördinate head and hand he has had a training which should enable him to go far in the practice of his chosen profession.

MICHIGAN'S PHARMACEUTICAL ACHIEVEMENT.*

BY C. H. STOCKING.[1]

"The following radio address by Professor C. H. Stocking, president of the American Association of Colleges of Pharmacy, will be of interest to all teachers of pharmacy. It gives a brief outline of pharmaceutical activity in the State of Michigan. I sincerely hope that Professor Stocking will, at a later time, write a complete history of this activity, and that the same will be done by leaders in other states of the Union. Such histories would be very valuable contributions to the Historical Section of the AMERICAN PHARMACEUTICAL ASSOCIATION."—C. B. JORDAN, *Editor*.

When James I of England in the 17th Century signed the corporate papers of the Apothecaries' Guild he said, "The business of the apothecary is a mystery: wherefore, I think it fitting that they should be a corporation of themselves." Pharmacists the world over may well look with pride and satisfaction to that early English monarch and his famous declaration. The impetus that was thus given to

* Radio address given over Station WJR, Saturday, January 28, 1933.

[1] Associate Professor, College of Pharmacy of the University of Michigan.

the development of the profession by the organization of the Apothecaries' Guild was destined eventually to project its influence across the seas to the great North American Continent that was then being so rapidly developed. English and European influence upon the practice of pharmacy in America underwent a gradual evolutionary change, ever influenced by the discovery from time to time of new and powerful indigenous drugs, until the turning of the tide which marked the time for a new vision of things. Through a gradual ascendance in pharmaceutical affairs, America eventually became the market place of the world for drugs and medicines and the mecca for those who would satisfy the thirst for education and research.

The Nineteenth Century marks the rapid development of pharmacy along more highly scientific lines than any previous period. It is also the period during which the names of American pharmacists first began to appear in the scientific and educational literature of the profession. It is probably unnecessary to state that the earliest historical events having to do with the advancement of pharmacy in America center around places and persons in the old colonial section of the nation. As civilization pressed its way westward with the onward march of progress, pharmacy was carried into newly conquered territory. Thus did Michigan come to figure in the "business of the apothecary" which King James referred to as the "mystery," or being interpreted into modern language, the "art, craft or profession" of pharmacy.

The practice of retail pharmacy, for instance, was established very early in the history of the state and has grown in importance with the steady increase in population until the present time when we find approximately 5000 registered pharmacists and more than 2500 retail drug stores within the borders of our commonwealth. Had the history of retail pharmacy in Michigan not been written in words that spelled success, the incentive that gave birth to our large pharmaceutical manufacturing plants would not have sprung into being. As early as 1855 the founder of the firm of Frederick Stearns and Company came to the city of Detroit, on New Year's Day, from Buffalo, with little money, fair credit and high hopes and established himself in retail and manufacturing pharmacy at Number Eight Woodward Avenue. Mr. Stearns' first laboratory was in a room twelve feet square located in the rear of his retail establishment. From this modest beginning has grown an institution that distributes its products throughout the nation and to the ports of most foreign countries.

Another example of successful pioneering in pharmaceutical manufacturing in Michigan is to be found in the history of Parke, Davis and Company. This famous firm with its world-wide reputation had its beginning in a drug store at the corner of Gratiot and Woodward Avenues, in Detroit, in the year 1862. The financial struggles of the next few years, we are told, may be imagined but can scarcely be described. It was not until 1866 that something resembling a permanent organization was effected. That year the partnership of Duffield, Parke and Company was formed and the date, October 26, 1866, has since that time been looked upon as the real birth date of the business. To-day the manufacturing and research laboratories of Parke, Davis and Company occupy literally many acres of floor space in Detroit. In addition to this they have a biological farm of practically 1000 acres near the city of Rochester, Michigan and branch houses in strategic points in the larger cities distributed over the globe. Time permitting, I could trace the origin

and development of other important and well-known pharmaceutical houses in the Detroit metropolitan area, including such firms as Nelson, Baker and Company, the Frederick F. Ingram Company and the Arthur Colton Company, manufacturers of pill and tablet machinery for the markets of the world. Traveling westward to the city of Kalamazoo we find the Upjohn Company which was established in 1866, by the late Doctor W. E. Upjohn under the original title of The Upjohn Pill and Granule Company. During the nearly half-century of its existence the Upjohn Company has experienced a steady growth due very largely to the development in its research laboratories of a number of important and effective therapeutic agents. Other organizations of a similar character to those just mentioned might be named to show that Michigan has been a leader in the field of manufacturing pharmacy for more than three-quarters of a century. To be sure, some firms have come and gone. Others have grown in size and importance until their influence is world-wide in character. Michigan has been a magic word for many decades when the source of manufactured, medicinal products has been considered. This inland state, remote from the crude drug markets of the nation, has built within its borders vast temples of healing that through commercial skill and scientific research have written their names in indelible letters on the pages of medical history.

Leaving this brief description of the history of manufacturing pharmacy within our state, let us look for a few moments at the early beginning of pharmaceutical education. In this regard, it is a noteworthy fact that the first institution of higher learning in the United States to include instruction in pharmacy in its curriculum was the University of Michigan. Referring to the meeting of the Board of Regents which was held October 2, 1839, we find that the governing body of the University even in that formative period of the history of the institution was not unmindful of the need for instruction in pharmacy, for during the course of their proceedings on that date they adopted the following resolution: "*Resolved*, That the appointment of Professor of Geology and Mineralogy in the University be tendered to Dr. Douglass Houghton, of Detroit, and that he be also charged with subjects of Chemistry and Pharmacy, till the Regents take further order in relation thereto."

A few years later the records show that Silas Hamilton Douglas was appointed Professor of Chemistry, Pharmacy, Medical Jurisprudence, Geology and Mineralogy, from 1851 to 1855; and that his title was changed to Professor of Chemistry, Mineralogy, Pharmacy and Toxicology from 1855 to 1870.

It was not, however, until 1868 that the first courses in pharmacy were incorporated as a regular part of the University curriculum. In 1876 the College of Pharmacy was organized with Doctor Albert B. Prescott as its first Dean. Following along in chronological order in other universities may be mentioned the fact that instruction in pharmacy was first offered at the University of Wisconsin in 1883; at Purdue in 1884; at the Universities of Iowa and Kansas in 1885. All of the Colleges of Pharmacy at these universities have administrative officers possessing degrees from the University of Michigan. From coast to coast, Michigan men, graduates of the College of Pharmacy, are to be found in the teaching profession and in research and administrative positions in commercial as well as in governmental laboratories. The thorough training which the University offers, amply prepares its graduates in pharmacy for positions of trust and responsibility in many important fields of endeavor. From the educational standpoint we antidate all other

universities in establishing instruction in pharmacy. Due to the thoroughness of this instruction and to the fact that the minimum four-year curriculum has been in vogue here since the early nineties, it is well-known that more deans of colleges of pharmacy and more faculty members holding positions throughout the nation have received their education at the University of Michigan than at any other institution of learning. In pharmaceutical organization work, Michigan men by the score have been highly honored. Of the thirty-two presidents of the American Association of Colleges of Pharmacy five have been members of the faculty and six others have received degrees from this University. Michigan men in large numbers are listed in the annals of United States Pharmacopœial and National Formulary revision work. If the "leaves of the trees are for the healing of the nation," Michigan men, Prescott, Stevens, Schlotterbeck, A. B. Lyons and others, have picked those leaves, have analyzed them for their medicinal virtues and have extracted their active principles for you and for me.

MODERN TRENDS IN EDUCATIONAL METHODS.*

BY A. B. LEMON.

More experiments and changes have been introduced in higher education in the last five years than in the previous twenty. The committee on educational methods of our National Conference on Pharmaceutical Research has been making a study of the major experiments in the field of higher education toward the end of selecting those the results of which might properly be used in pharmaceutical education. This paper is intended briefly to present some observations on a few of the educational problems receiving most wide-spread attention and showing most promising results. This may be considered a supplement to the less detailed report read before the conference last Saturday.

Experimentation has been very active in all four branches of education, *viz.*, care and direction of students, curriculum construction, teaching methods and administration. The National Society of College Teachers of Education has just published a wealth of material on changes and experiments in liberal arts education collected and organized by the American Association of University Women under the able direction of Kathryn McHale. This report gives, in addition to other valuable information, a summary of one hundred twenty-eight outstanding changes and experiments in higher education as selected by C. S. Boucher of the University of Chicago. From this elaborate list six topics have been chosen for discussion in this paper. These have been selected first because of the interest they should demand in pharmaceutical education and second on the basis of the number of colleges experimenting with them. The six selected are as follows:

(1) Comprehensive examinations [115].
(2) Admission of freshmen including tests [104].
(3) Honors courses [100].
(4) Personnel work including counseling of students [83].
(5) Improvement in curricula [63].
(6) Improvement in teaching methods [45].

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* Section on Education and Legislation, A. PH. A., Toronto meeting, 1932.

The number in brackets indicates the number of liberal arts colleges experimenting with the project as reported by the A. A. U. W. survey.

Comprehensive Examinations.—It is not surprizing to find the subject of examinations leading the list of experiments. The old *essay type* of examination as a single measurement of learning has been subject to sharp attack for some years. Its extreme subjectivity both in construction and reading, its narrowness of sampling and its demoralizing influence on both teacher and student stand out most prominently among its negative values. Of course the essay type is not without some positive values but they are largely confined to a measurement of composition and English which may or may not be found among the objectives of the particular test involved. Certainly testing for breadth and readiness of information should be left largely to other types of examination. In so far as *oral examinations* are concerned Ben Wood states that they are for the most part "highly ambiguous in purpose, methods and results." The *objective or new type examination* is being used very extensively as a supplement to the essay type. The new type examinations have their critics, too, but most of the valid criticism is leveled at their composition and administration rather than at the principle involved. And now comes the *comprehensive examination* which is not a type of examination but rather a different application of the types already available and mentioned above. Comprehensive examinations are, as the title suggests, tests that cover large fields of thought rather than small course units. They are now being used in more than one hundred American colleges and according to reports the results are highly gratifying. While there has been a marked trend toward a mixture of types of tests followed at the end of the course by a comprehensive examination the most important move, in so far as the usual examination is concerned, has been toward the development of objectivity. Never before has there been such profound recognition of the fact that the fundamental task in the construction of an achievement test is to make certain that it is an adequate measure of the important objectives of the course. "What do we want to measure" should be the question constantly before us. For instance, in Botany the following course objectives might be set up toward which the student would progress:

(1) A fund of information regarding plant structure.
(2) An understanding of technical terminology.
(3) An ability to draw inferences from facts.
(4) An ability to apply principles to new situations.
(5) Accuracy of observation.
(6) Skill in the use of the microscope and other essential tools.
(7) An ability to express effectively ideas relating to Botany.

The nature of these objectives determines the variety of the test to be constructed. The individual being tested should, at the end of the test, see as clearly as does the examiner what the results mean. Examinations should be made to benefit the examined as well as the examiner, and every test to have a constructive influence upon the student should yield an accurate measurement which can be arrived at only by objective means. Many of the examinations now given in American Schools lay too much stress on the learner's memory for facts and his ability to define technical terms. In so far as such tests serve as the means of selecting those who

should be advanced they emphasize or select memory as the most desirable or at least the most tangible trait to be cultivated through the educational process. It is a grave question as to whether the ability to draw inferences is equally if not more important than the ability to remember. The application of comprehensive examinations in colleges of pharmacy might well be undertaken. Indeed, at least two schools are now using them in a limited way. The author has used a comprehensive test in Bacteriology on a selected group of seniors during the past three years with gratifying results to both student and examiner. We know of no instance, however, in which a comprehensive examination covering the entire course is given to pharmacy students at the end of their course. That is the way it is applied in liberal arts colleges and usually is a complement of some sort of honors course or tutorial system. Professor E. S. Jones of the University of Buffalo has just completed an intensive study of the merits of comprehensive examinations for the American Association of Colleges. His report published by the A. A. C. is heartily commended to those interested in this project.

Admission of Freshmen Including Tests.—Shall we admit all candidates to our courses who meet the minimum requirements, *viz.*, high school graduation, or shall we refuse admission to those who do not look promising? If so what will be the basis for our eliminations? Unfortunately we are not yet in possession of any single safe device or formula that can be relied upon to sift the chaff from the wheat. From an academic standpoint the candidate who comes from the lowest two-fifths in his high school and who receives a low score in any of the standard intelligence tests is a "poor risk." In the liberal arts college of the University of Buffalo *all* applicants from the lowest two-fifths in high school and those of the middle fifth who do not have a good score on an intelligence test are required to take a three-week preliminary study course known as a "How to Study Course." This course is designed *first* to test thoroughly the ability of these so-called "poor risks" to undertake college work and *second*, to train them in the techniques of study. This course has been required since 1926, and the results have been very gratifying. The percentage of these "poor risks" in the entering class has dropped from 20% to 12%, the percentage of individuals surviving the freshman year with an average of "C" or better has been doubled and the total of failures has been reduced from 40% to 15%. This program appears to be the most elaborate used by any college for the admission of "poor risks." Of course, each of the 144 colleges reporting in the A. A. U. W. report has a testing system. Indeed the results of two or three aptitude tests plus the high school record are almost indispensable, not so much for determining eligibility for admission as for dealing with the student after he is in college. This subject was covered in detail in a paper entitled "Five Years of Intelligence Testing" read at Miami last summer. Most of the older colleges such as Harvard require their freshmen to pass a college entrance examination. Personal interview of entering students is practiced at a number of institutions. Colgate and Rollins report enthusiastically on the benefits of a personal interview. The Rollins interview is supplemented by elaborate questionnaires filled out by teachers, employers, parents and the applicant.

The trend in this field is distinctly toward a more careful selection of candidates for higher education and improved means for making the selection. It is considered eminently unfair to accept a candidate whose failure in a particular field is a

foregone conclusion. It is equally unfair to society and the profession to accept a thoroughly unfit candidate and then push him through just for the sake of the tuition he pays.

HONORS COURSES.

During the last ten years there has been a tendency on the part of a number of American colleges, at first limited to Harvard, Princeton, Smith and Swarthmore, to utilize modifications of the honors system and tutorial methods long used by Oxford and Cambridge. The basic principles of the American adaptations seem to be

(1) The college student should learn to educate himself.
(2) The student should receive more individual contact, guidance and stimulus from his teachers.
(3) Superior students should receive some marked recognition of their superiority other than that usually conferred at graduation.
(4) The student should be tested at the end of his college course with examinations covering the whole field of his concentration.

While there are more than one hundred colleges now using some modification of the honors system, Swarthmore has been the pioneer in this field and has perhaps received more attention than any other American college. Honors work was begun there in 1922. The story of its progress is splendidly recorded in a book by Robert C. Brooks entitled "Reading for Honors at Swarthmore." Honors students are selected from the upper classmen after showing a marked superiority in their freshman and sophmore years. As a merit for their excellency they are permitted more or less latitude in their class attendance and study hours. There are set hours for group conferences with the professors. These conferences may be held two or three times weekly. The professor acts as one of the students rather than as a schoolmaster. The questioning and debate and the personal contact between professor and student are said to be very stimulating to both. There is no reason why some modification of the honors system should not be used in pharmacy schools. Experience has shown that it is not only beneficial to the upper classmen participating but it also stimulates more underclassmen to a greater effort in their desire to qualify for the benefits and privileges of the "honors group." It has also proved a valuable means for stimulating desire to do graduate work—a stimulus badly needed in pharmacy schools. At the University of Buffalo School of Pharmacy we have been able to show repeatedly that superior students are not motivated to their best efforts when given no more work than can be accomplished by the average or inferior group. The result is that they either do more outside work or waste the time that might be spent in advanced work if opportunity were presented. Undoubtedly the best method for stimulating the average boy to additional effort is to reward him for work well done. The "honors work" has proved to be a highly satisfactory reward.

Personnel Work Including Consulting Students.—With the advent of the wide elective system in our arts colleges it became necessary to have some office responsible for the guidance of students in the selection of proper courses. The duties of this office have been broadened out to include vocational guidance, the analysis and remedying of student difficulties, the administration and analysis of various

tests and the correlation of test results with college grades. Some personnel offices serve as placement bureaus. Heretofore the bulk of the duties enumerated above have been the responsibility of the college Dean. The trend, however, is toward placing these details in the hands of one or more members of the faculty who by training and temperament are especially fitted to deal with students in a personal and friendly way. It is obvious that up to the present time pharmacy students have not needed guidance in the selection of electives because there have been none. Nor has he had any vocational guidance, since by entering a professional school he has thereby selected his vocation whether qualified for it or not. With the advent of the four-year curriculum and its proposed electives there will now be a demand for assistance in selecting the proper courses. The personnel record of each pharmacy student should include

(1) Results of aptitude and placement tests.
(2) High school record.
(3) College record to date.
(4) Health record.
(5) Amount of outside work.
(6) Extra curriculum activities.
(7) An analysis of personal traits.
(8) Such other available information as will assist in giving the student as well as the faculty the most useful information when needed.

The personnel office is now recognized by most colleges as an indispensable part of their equipment.

Improvement in Curricula.—The most recent trend in curriculum construction is the development of a course of study based upon the exact needs of the student. Curriculum builders are constantly asking themselves this question—what does this student need to know intelligently to pursue his chosen calling—and then building his course to suit his needs. The recent work of Charters and his associates has given us the basic material for a pharmaceutical curriculum. Since we are all familiar with that work and since it represents the most modern methods of curriculum construction, it will be unnecessary further to discuss it in this paper.

Improvement in Teaching Methods.—The Boucher survey, mentioned earlier, reports forty-five colleges experimenting with improvements in instruction. The most outstanding work has been done at Yale, Rollins, Illinois, Oberlin, Purdue and Chicago. Reports of success have been widely disseminated through educational publications and college reports. The American Association of University Professors under the direction of Professor H. L. Dodge of the University of Oklahoma is just now completing a survey of the teaching practices in vogue at our leading colleges. When this survey is complete a group of experts will evaluate the various teaching methods and report thereon. This report should be one of profound interest to pharmaceutical educators.

Obviously it will be impossible to even enumerate in this paper the vast number of methods being employed to improve teaching. The application of much already discussed in this paper has in a general way improved our teaching. Much remains to be done. A number of colleges have thrown the spot light on their teaching defects through self surveys. If discreetly conducted, a faculty can critically examine its own teaching procedure without creating any internal ill will. A real teacher

does not object to being shown a better way to teach. The opinions of students and alumni should be solicited but carefully evaluated before being accepted. In the author's school the faculty annually elects a committee on teaching methods. The members of this committee are expected to be familiar with advocated improvements in teaching. A portion of each faculty meeting is devoted to a discussion of some phase of teaching such as "Methods for Securing Student Interest," "Modern Methods for Testing Achievement," "The Values of Personal Interviews," etc. One school of pharmacy maintains a library of the most recent books and articles dealing with teaching methods for the use of its faculty. One of the most significant trends in the improvement of teaching in pharmacy schools is the marked improvement in the quality of our younger teachers. Pharmacy schools are now beginning to demand the same degree of excellency in their teachers as is required in other branches of higher learning.

SUMMARY.

Hundreds of experiments are being conducted in an effort to improve our educational methods. The last decade has seen the application of the results of such experiments with exceedingly gratifying results. Some of these modern methods in education should be introduced in pharmaceutical training. This paper suggests six projects for consideration by pharmaceutical educators. They have produced outstanding results in liberal arts colleges and should at least be tried by us. It is recommended that in those schools where the Dean does not have the time to review the literature on educational methods an individual or committee be charged with that responsibility in order that our faculties may know what is going on even though they may not agree with or be in position to apply advocated changes.

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PHARMACY AS A CAREER.

Herbert Skinner, chairman of the British Pharmaceutical Conference, who was a welcome visitor at the Toronto A. PH. A. meeting is reporting on his visit in *The Chemist and Druggist*. Referring to the *Guidance Leaflet* of the United States—he states "it presents an idea for pharmacy well worth while and quotes: 'Collegiate education and training is designed to prepare the pharmacists to conduct a pharmacy, to prepare, compound, distribute and dispense drugs and medicines, including narcotics, poisons and alcoholic liquors; to furnish sick room supplies; to distribute insecticides and fungicides; to make analytical and microscopic examinations and service; and to do these on sound economic principles.' "

COMMITTEE REPORTS

REPORT ON THE PAN-AMERICAN MEDICAL CONGRESS.

BY THEODORE J. BRADLEY.

The fourth congress of the Pan-American Medical Association at Dallas, Texas, March 21st–25th, was attended by hundreds of members and delegates from North and South America and the West Indies. This organization is devoted to the scientific aspects of medicine and allied sciences, and its previous meetings were held in Mexico City, Panama and Havana, Cuba. The next meeting is to be held in Caracas, Venezuela, probably in January 1935.

The United States Pharmacopœial Revision Committee was represented at the Congress by Dean Theodore J. Bradley of the Massachusetts College of Pharmacy, chairman of Sub-Committee No. 14 of the Pharmacopœial Revision Committee, who served as acting chairman of the Section of Pharmacopœias, in the absence of the chairman, Dr. Francisco Hidalgo of Cuba. The secretary of the Section was Dr. L. W. Fetzer, of Dallas.

In his address as chairman, Dean Bradley presented, "Some Thoughts on the Future Relationships of the Pharmacopœias of the Americas" and suggested the creation of a Pan-American Committee on Pharmacopœias, whose duty it would be to recommend steps to reconcile differences between the different American Pharmacopœias, and which should consider the preparation of a digest of the different American Pharmacopœias, to be published in both English and Spanish.

The Section on Pharmacopœias held three sessions during the Congress, at which a number of papers, prepared by members of the Revision Committee and others, were presented, including the following:

1. "Pan-American Pharmacopœial Uniformity," by E. Fullerton Cook, chairman of the Committee of Revision of the Pharmacopœia of the United States.
2. "Pan-American Drug Standards," by E. L. Newcomb, P.D., chairman of the Sub-Committee on Botany and Pharmacognosy of the Committee of Revision of the Pharmacopœia of the United States.
3. "Biological Products for the Forthcoming Revision of the U. S. Pharmacopœia," by George W. McCoy, M.D., chairman of the Sub-Committee on Biological Products of the U. S. P. Committee of Revision, and Director of the National Institute of Public Health, Washington, D. C.
4. "Thirty American Medicinal Plants, Parts I and II," by Felipe Urquieta, Sc.D., P.D., Arequipa, Peru.
5. "Some Difficulties Encountered in the Assay of Hyoscyamus," by H. G. DeKay and C. B. Jordan, chairman of Sub-Committee on Proximate Assays of the U. S. Pharmacopœia, eleventh Revision.
6. "Pharmacopœial Standardization of Medicinal Chemicals," by George D. Beal, P.D., Ph.D., Assistant Director, Mellon Institute of Industrial Research, chairman Sub-Committee on Organic Chemicals, United States Pharmacopœia, Committee of Revision.
7. "Alcohol in the Important Pharmacopœias of the World," by Charles H. LaWall, Ph.M., Sc.D., chairman of the Sub-Committee on Volatile Oils, Committee of Revision, U. S. Pharmacopœia; and Amelia Mesa Ponce, P.D., Member Cuban Auxiliary Commission, U. S. Pharmacopœia, Eleventh Revision.
8. "Distilled and Potable Waters in the Important Pharmacopœias of the World," by Charles H. LaWall, Ph.M., Sc.D., and Amelia Mesa Ponce, P.D.
9. "The Determination of Hydrogen-Ion Concentration in Its Relationship to a National Pharmacopœia," by John C. Krantz, Jr., chairman of Sub-Committee on Inorganic Chemicals of the U. S. Pharmacopœia, Eleventh Revision.
10. "Pharmacopœial Ointments," by Leonard A. Seltzer, Sc.D., Detroit, Michigan, chairman of U. S. P. Sub-Committee on Galenicals.
11. "A Method for the Biological Assay of Drugs That Depress the Nervous System," by James C. Munch, Ph.D., and Amelia Mesa Ponce, P.D., Biological Laboratories of Sharp and Dohme, Glenolden, Pa.

12. "Pan-American Medical Congresses as Agencies for Stopping the Gap between Medicine and Pharmacy," by Lewis W. Fetzer, Ph.D., M.D., Sc.D., Dallas, Texas.

Typewritten copies of nearly all of the papers, with translations into Spanish by Dr. Amelia Mesa Ponce, were distributed to the delegates in attendance when the papers were read. It is felt that a great deal was done at the meeting to secure and maintain the highly desirable uniformity among the present and prospective pharmacopœias of the various countries in the western hemisphere.

SUPPLEMENTARY REPORT.

Word has been received from Dr. Francisco Hidalgo, of Havana, Cuba, who had been appointed chairman of the Section on Pharmacopœias but was unable to attend the meeting in Dallas, that the following additional papers have been contributed to the Pharmacopœial Section and will be published.

1. "Concept of the Pharmacopœia," by Dr. José C. Diaz, of Havana.
2. "The United States Pharmacopœia and the Projected Pan-American Pharmacopœia," by Dr. Francisco Hidalgo.
3. "Considerations in Regard to the Translation into Spanish of the United States Pharmacopœia," by Dr. José Capote Diaz, of Havana.
4. "Official Pharmacopœias and Formularies of the American Continent. Introductory Study for a Projected Pan-American Pharmacopœia," by Dr. Ricardo Galbis, of Havana.
5. "The Pan-American Pharmacopœia," by Dr. Francisco Velez Salas of Caracas, Venezuela.

OFFICIAL PHARMACOPŒIAS AND FORMULARIES IN USE IN THE DIFFERENT COUNTRIES OF AMERICA.

PRELIMINARY SKETCH TO BE USED FOR THE CREATION OF A PAN-AMERICAN PHARMACOPŒIA.

BY DR. RICARDO GALBIS.

We, the people of the various countries of America, know each other less than the inhabitants of distant continents. We mind more European affairs than our Pan-American cultural development, being thus careless about the cultural status of our neighboring countries.

With reference to the Pharmacopœias, which are of vital importance in all health problems, we must admit that many are ignorant as to the type of Pharmacopœia, either official or in use, employed by their respective neighbors.

The object of the present sketch is to investigate which are the official pharmacopœias and formularies in use in the different countries within the American Continent and with this information adopt a policy which will regulate the construction of The Pan-American Pharmacopœia, discussing at the same time its advantages and disadvantages.

The data for this sketch have been obtained from official sources, such as: Bureau of Foreign Relations, Public Health Board, universities, scientific reviews, professors, individual authorities, etc. (The author desires to be reminded of any misquotation, misrepresentation or errors regarding the body of this work, and invites the reader to make suggestions, for it will be for common interest.)

Our information is not limited to American political units, for it also covers data from European possessions in America. The European possessions in America not quoted in this work are understood to be using the official pharmacopœia of their respective commonwealths.

In accordance with the above we come to the following conclusion: Out of the twenty-one independent republics of America, six have their own pharmacopœia: United States of America, Mexico, Venezuela, Brazil, Argentine and Chile. The following possess their own formulary: Canada, United States of America and Cuba. Eleven countries lacking a local pharmacopœia have adopted the French Pharmacopœia; five have adopted the Pharmacopœia of the United States of America. (In accordance with the information received Nicaragua has adopted as official both the French and the United States pharmacopœias, which information must be, in due time, verified.)

As a final analysis of this subject it is a proved fact that the editing of a Pan-American Pharmacopœia should include among its various chapters a thorough treatise on all medicines which are widely recognized for their therapeutic efficiency and general usage. This work might represent a worthy contribution to the progress of the profession in America. Some one may raise the objection that native medicaments of a given country cannot be materially employed in other countries, and the description of the numerous native medicaments of different countries would unnecessarily increase the volume of this work, lacking as well in practical value. We must argue, in answer to that objection, the Pan-American Pharmacopœia would only contain the medicaments possessing uniform and well-defined effects and in general usage in America, and we would set aside for another official work such as the National Formulary for each country, herein dealing with native medicaments as regards each country. If out of the twenty-one American republics only six possess their own pharmacopœia and out of these six we find some that have had no revision for a long time or do not meet the requirements of a true pharmacopœia, is it not a logical conclusion to entertain the project of editing a Pan-American Pharmacopœia?

OFFICIAL PHARMACOPŒIAS.

Country.	National Pharmacopœia.	Adopted Pharmacopœia.
United States of America	Pharmacopœia of the United States of America, Tenth Decennial Revision, 1926	
Mexico	Farmacopea Nacional Mexicana, 1930	
Cuba		United States
Santo Domingo		United States
Haiti		French
Guatemala		French
Honduras		French
Nicaragua		U. S. P. and French
El Salvador		French
Costa Rica		United States
Panama		United States
Colombia		French
Venezuela	(Third Edition) Farmacopea Venezolana, 1927	
Ecuador		French
Brazil	Pharmacopeia dos Estados Unidos do Brasil, 1929	
Peru		French
Bolivia		French
Paraguay		French
Argentina	Farmacopea Argentina, 1928. Second Edition	
Uruguay		French
Chile	Framacopea Chilena, 1905	

This would represent continental coöperation of the highest order as the natural result of the organized efforts of countries united by both geographical and historical ties. We must consider in our favor all of the agreements taken at Pan-American congresses and international sanitary Conventions of American republics. The Second Pan-American Congress held at Mexico City thirty-five years ago agreed that each country present would designate a sub-committee out of its members, and these sub-committees would coöperate in editing a Pan-American Pharmacopœia, which work was supposed to be recognized as official by the governments represented at the Congress. At that Congress Professor Joseph P. Remington's exposition on a Pan-American Pharmacopœia was presented and also Dr. H. H. Rusby's work entitled "Pan-American Flora." At the Second International Sanitary Convention of the American Republics held at Washington in the year 1905 it was agreed to translate into Spanish the Pharmacopœia of the United States of America, which translation was to be presented to the Spanish-speaking countries with the object of adopting it as the official Pan-American Pharmacopœia. At the seventh convention of the same body held at Havana in 1924 fundamental agreements were taken as to prospec-

tive food and drugs laws to be adopted by each country. And, finally, the Third Pan-American Medical Congress held at Mexico City in July 1931 agreed to designate a board to take charge, after obtaining the sanction of their respective governments and the Revision Committee of the Pharmacopœia of the United States, of editing a Pan-American Pharmacopœia. This proposition was made by Dr. Demetrio Lopez, as president of the Mexican Medical Academy.

If the scheme for a universal or else international pharmacopœia has been sustained and commended by recognized authorities, all the more logical the existence of a Pan-American Pharmacopœia. The agreements and objects of all conferences dealing with the unification of the formulas for active medicaments, and taking into consideration the pharmacopœias of advanced countries, these might be used for the plan of editing a Pan-American Pharmacopœia.

It must be noted that the Spanish Pharmacopœia has never been officially adopted by any of the nations within the American Continent, as might be expected for historical reasons. This experience proves that the Spanish Pharmacopœia was considered inadequate at the time the Spanish-speaking countries adopted either the French or the United States Pharmacopœia.

With the advent of the eighth edition of the Spanish Pharmacopœia and the rise of the Spanish Republic it might be expected that Spain might try to reconquer Spanish America as regards intellectual tradition, in the pharmacopœial sphere.

San Lazaro 331,
Habana, Cuba.

PAN-AMERICAN PHARMACOPŒIAL UNIFORMITY.

BY E. FULLERTON COOK, PH.M.*

The establishment of a Section on Pharmacopœias as a regular function of this Association opens a new line of interest and service in Pan-American coöperation which is most gratifying. The idea of a Pan-American Pharmacopœia and in fact the effort to develop an "International Pharmacopœia" is not new, but every earlier effort failed because such an idea is not in conformity with the spirit of strong nationalism which exists in every country. We may well benefit from the experience of the international groups who made their first progress by agreeing upon a policy which did not interfere with the continuance of their own national Pharmacopœia but, in principle, obtained practically all of the benefits of an "International Pharmacopœia."

I am suggesting, therefore, that this Section agree upon a series of principles, expressed by appropriate resolutions, which should interest the health departments of all of the Republics associated in the Pan-American Union and stimulate activity toward a uniformity in the standards for the more important medicines used by all.

The plan proposed would embody the following general principles:

In recognition of the fact that a number of the Republics associated in the Pan-American Union have already established their own national Pharmacopœias, through the professional cooperation of physicians and pharmacists in their own country, and that others plan to do so as soon as conditions permit, and, since such a policy is desirable in that it enables each country to best provide for its own special needs, and also stimulates interest and development in many associated sciences, it is therefore recommended:

1. That an effort be made to reach a Pan-American agreement upon the standards of strength and purity for the more important therapeutic agents and aids employed by physicians in these associated countries.
2. That a "Committee on Pharmacopœial Uniformity" be created, the authorities in each Republic being invited to name a representative on the Committee.
3. That the aid of the offices and facilities of the Pan-American Health Union at Washington be enlisted for the purpose of obtaining contacts with the various Health Departments of the Republics in the Union and that the aid of their journal be requested as a means of publicity and information.

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* Chairman of the Committee of Revision of the Pharmacopœia of the United States. Read at the meeting of the Pan-American Medical Association, Pharmacopœial Section, held at Dallas, Texas, March 21–25, 1933.

4. That this Committee on Pharmacopœial Information, through the aid of its members, assemble lists of about 400 of the most frequently prescribed medicinal substances in each country, arranged in the order of frequency of use, and, from these compilations, the Committee determine those substances which are almost universally used.
5. Having obtained this list of therapeutic substances, employed in the treatment of disease, by practically all countries, a united effort should be made to agree upon the adoption of suitable titles and synonyms acceptable to all, upon uniform strengths and percentages of purity and even upon tests and assays.

If such agreements can be reached the essential advantages of a Pan-American Pharmacopœia will have been attained. Each country, as it revises or establishes its own Pharmacopœia, will have these agreed-upon standards for inclusion, if they so elect, and thus bring about a uniformity which is greatly needed on this Continent as we develop close social and business relationships.

It is hoped that out of this year's meeting there may be planted a seed of coöperation, through the erection of a Pan-American Committee of the type suggested which may grow lustily and report substantial progress at the next meeting of this Pharmacopœial Section.

PRESCRIPTION TOLERANCES.*

In most states of the Union there is some law-enforcement body with supervision over the quality of drugs, preparations and prescriptions furnished by pharmacists. The protection of public health is the prime object of such supervision but it is also of great advantage to the pharmacists. This latter fact is probably not sufficiently appreciated. The protection it affords to the standing of professional pharmacy is obvious, but the commercial aspect should not be overlooked. If there were no control of the quality of drugs the doors would be wide open to harmful competition. Prices could be lowered at the expense of quality, the public would suffer, and the rank and file of conscientious pharmacists would be at a great disadvantage.

Fortunately, this control work is in most instances in the hands of Boards of Pharmacy or other groups sufficiently familiar with prescription practice to know what degree of accuracy can be reasonably expected in compounding. There are, however, occasional instances which result in much discredit to the pharmaceutical profession because of the lack of such knowledge. Prescriptions compounded most carefully will upon chemical analysis be found to vary slightly in the quantities of ingredients from those prescribed. Such variations are due to various factors, many of them beyond the control of the compounder, and when not given proper consideration by law-enforcement bodies, injustices may follow. This is particularly true when the results are given to the lay press without explanation. In many instances, the percentage deviation is never mentioned but simply recorded as "deficient," "sub-standard" or "super-standard."

The AMERICAN PHARMACEUTICAL ASSOCIATION at its last meeting voted the appointment of a Committee on Prescription Tolerances to make a study of what constitutes reasonable deviations in prescription ingredients and to establish reasonable tolerances. Tolerances are permitted in many official and unofficial preparations and they would seem equally necessary in prescriptions which in emergency cases are usually made extemporaneously and frequently hurriedly. The members appointed by President Philip are Chairman, Hugo H. Schaefer, Phar.D., Ph.D., Professor of Analytical Chemistry of Columbia University, College of Pharmacy; Samuel L. Hilton, Ph.M., Phar.D., Retail Pharmacist and Treasurer of the Pharmacopœial Convention, and Robert L. Swain, Phar.D., LL.B., Deputy State Food and Drug Commissioner of Maryland and Secretary of the Board of Pharmacy. This Committee proposes to first make a general survey of tolerances now allowed by the various pharmaceutical law-enforcement bodies and secondly to study the factors which cause deviations in prescription quantities.

To accomplish the first of these objects, the coöperation of state boards of pharmacy, state association secretaries, law-enforcement officials, and others interested will be sought in order to determine the views and practices now in vogue. A study of such data should go far in deter-

* Bulletin No. 12, AMERICAN PHARMACEUTICAL ASSOCIATION, May 12th.

mining proper prescription tolerances. The second phase of the work, that of studying and analyzing the various causes of deviations and determining reasonable degrees of such deviations, is a difficult problem, since each type of prescription—liquids, powders, pills, capsules, ointments, etc.—will require a separate study. In the case of liquids some of the factors to be considered are:

a. Moisture and allowable impurities in chemicals.
b. Unavoidable inaccuracies in weighing and measuring.
c. Unavoidable losses due to a portion of the ingredients remaining in or adhering to utensils.
d. Decomposition and deterioration.

In the case of ointments, the same factors are present but to different degrees. With powders, pills and capsules there will be additional variations in the weights of the individual units of the prescription. In these studies, the coöperation of pharmaceutical organizations will be sought in obtaining samples, etc.

The Committee is receiving the coöperation of the Food and Drug Administration, U. S. Department of Agriculture, and Dr. W. G. Campbell, Chief of this Bureau, has expressed great interest in the work and objects of this Committee. It is hoped that the extensive study of prescription compounding will lead to satisfactory conclusions and will result in tolerances acceptable to all law-enforcement bodies and at the same time not be burdensome to the pharmacists nor unfair to the public.

NATIONAL CONFERENCE ON PHARMACEUTICAL RESEARCH.

To the Chairmen and Committeemen of the National Conference on Pharmaceutical Research: The calendar and the increasing warmth of the weather indicate that the time has arrived for the annual call to the committees of the National Conference on Pharmaceutical Research to prepare for the annual sessions of the Conference which will occur this year at Madison, Wisconsin, on Saturday, August 26th.

If it is not too inconvenient will you please hunt up your desk copy of the Proceedings of the N. C. P. R., 1931–1932, and note on page two the general heading indicating that the ten committees are *to review the research achievements in the profession of Pharmacy for the year September 1, 1932 to August 31, 1933.*

Secretary Krantz has recently assured me that with the prospective general inflation in all activities in our nation, he believes this year to be propitious for the enlargement of our annual publication by a considerable number of pages and an addition to the title indicating that it contains "The Annual Review of Pharmaceutical Research."

Therefore, I am making a direct appeal to each of you to meet this new issue squarely and to provide the best possible material for this first volume of "The Annual Review of Pharmaceutical Research."

In the 1932 Proceedings the Committee Reports begin on page 18 and continue to page 47, a total of 30 pages. If we were to double this section with no increase in the other sections, it would increase the total pages to 98, and thus make the publication a book. I feel confident that we can financially afford to do this and that we should present an American publication giving a comprehensive and very readable report on the annual progress in Pharmacy.

We do not want a book of abstracts nor one of dry statistics; but we do want ten short chapters reflecting the combined knowledge and judgment of each of the ten Committees standing back of their respective chairmen; we want to recognize when we have read these ten reports that our attention has been called to the striking discoveries and the leading events in each of these ten fields of pharmacy; we want to feel refreshed and somewhat entertained and especially to be strongly inspired regarding the present and the future progress of pharmacy; and we want to make known, not only to the younger scientific men in pharmacy and throughout the pharmaceutical field, but also to the scientific world in general, the fact that there are annual research achievements in pharmacy.

The chairmen, of course, must take the lead in preparing the Committee Report, but every

committeeman should help his chairman by offering suggestions for the report and by reading it critically after it has been prepared by the chairman.

Trusting that each Committee will engage promptly in the preparation of this report and looking forward to an especially good meeting at Madison, Wisconsin, this year, I remain

E. N. GATHERCOAL, *Chairman.*

May 13, 1933.

MOUNDS IN WISCONSIN.

(This article and that in the April JOURNAL should be credited to the author—Charles E. Brown, Chief of the State Historical Museum.)

Systematic archeological research and investigation in Wisconsin were begun by Dr. Increase A. Lapham at Milwaukee in 1836, assisted financially by the American Antiquarian Society of Worcester, Massachusetts. He extended his surveys to other parts of the state. In 1855 the Smithsonian Institution at Washington, published his classic, finely illustrated report, "The Antiquities of Wisconsin." In 1836 he found at Waukesha and described the first effigy or animal-shaped, a figure representing the turtle.

Since the year 1901 the Wisconsin Archeological Society has been engaged in locating, mapping and exploring the Indian mounds, enclosures, village sites, cemeteries, planting grounds, mines and quarries, shrines, trails and other features of the state. Of mounds and other earthworks the Society has located 12,000 specimens, a far larger number than probably existed in any other state east of the Mississippi River. Six thousand are reported as found in Ohio.

These Wisconsin mounds are largely conical, oval, linear and effigy mounds. Some flat-topped, platform and cairn mounds have been also located. Also a number of enclosures of circular, semi-circular, oval, square, octagonal and oval and other forms. Large groups of conical, linear and effigy mounds formerly existed or still exist at Milwaukee, Racine, Burlington, Waukesha, Oconomowoc, Pewaukee, Delevan, Beloit, Janesville, Lake Kodhkonong, Ft. Atkinson, Lake Mills, Madison, Baraboo, Devil's Lake, Prairie du Chien, La Crosse, Trempealeau, Kilbourn Packwaukee, Green Lake, Waupaca, New Lisbon, Menasha, Green Bay, Lake Chetek, Rice Lake and in other places in the state. Many of these have been destroyed by the growth of cities and from other causes. Others have been preserved to the public in county, city and state parks and in other public properties and are visited by hundreds of thousands of citizens and tourists every year.

Particularly notable among the mounds and other earthworks of Wisconsin are the great earthwork enclosure at Aztalan, near Lake Mills, the site of a prehistoric stockage-protected settlement of Indians of the Cahokia or Middle Mississippi valley culture, the intaglio effigy mound in River Park at Fort Atkinson, the mound group on the campus of Beloit College, the huge bird effigy mounds on the State Hospital grounds at Mendota, the bird effigy in Devil's Lake State Park, and the great Man Mound in Man Mound Park at Baraboo.

The modes of burial in Wisconsin mounds are of a number of distinct kinds: 1. Full length burials, the skeletons lying on their backs; 2. Flexed or folded burials, the arms being bent, and the legs drawn up or beneath the body; 3. Burials made in a seated or crouching position; 4. Bone burials or re-burials, the bones of the dead being removed from temporary burial places and placed on the ground in bundles or small heaps; 5. Mass burials, the bones of a number or large number of individuals being thrown together or placed in a large heap. Cremation was also practiced by the prehistoric Indian inhabitants of Wisconsin, the bodies or bones being partly or wholly incinerated and a mound constructed over them. Burial pits or stone or wooden vaults to contain the bones of the dead were constructed. Interred with the remains of the dead in some mounds are the beads and ornaments, pipes, weapons, pottery vessels and other objects for their use in their journey to the spirit world. Many bodies were no doubt wrapped in bark, cloth or skins when buried.

NEW JERSEY ASSOCIATION.

The sixty-third annual meeting of the New Jersey Pharmaceutical Association will be held at Asbury Park, June 14th–16th.

Among the speakers at the banquet will be President-Elect Robert L. Swain, of the AMERICAN PHARMACEUTICAL ASSOCIATION.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter.

CHICAGO.

The 213th meeting of the Chicago Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on Tuesday evening, April 18, 1933, at the University of Illinois College of Pharmacy.

The speaker of the evening was H. C. Christensen, director of the Pharmacy exhibit at the Century of Progress Exposition. Mr. Christensen gave the large audience assembled a very clear insight into the part that Pharmacy will have in the coming Century of Progress Exposition that will open in the city of Chicago on June 1, 1933.

A futuristic sketch of the Hall of Science Building, which will house the Pharmacy exhibit, was placed in view of all and many references were made to it so that we might become acquainted with the positions of the many exhibits connected with pharmacy. It was pointed out that the aim of the Pharmacy exhibit was to bring to the attention of the general public the service that pharmacy renders.

The advantage of the training in pharmacy that we get now in comparison to that we received years ago will be brought clearly to the attention of the public. It is hoped to inspire those now in training to feel that pharmacy is a profession.

This fair is a fair to show the progress that has been made in the last one hundred years; it is more than a fair to show the competitive angle.

Pharmacy will have what is thought to be a choice location in the Hall of Science Building. There have been 1700 sq. ft. of space allotted to the Pharmacy exhibit. This space, which has been donated, has a value of $17,000. The exhibit will be on the first floor. As people enter the building their first view will be of historical matter, then a reproduction of the first retail pharmacy in Chicago. Passing on from the old pharmacy one will see a pharmaceutical and chemical laboratory, showing prescription filling, chemical tests, etc. Then will follow: a U. S. P. and N. F. display; a display of digitalis, showing the steps involved from the growing plant up to the finished tincture; an educational section showing materia medica exhibits, service to the public, etc., with emphasis on the increased requirements needed to become a Registered Pharmacist.

It was mentioned that this non-commercial exhibit is being financed solely by contributions and that there has been some trouble in getting the money needed, although enough donations have been received to put the exhibit in order for the opening. More money will be needed to finance the running of the exhibit, however, and those who wish to contribute will be rewarded by having their names printed on a chart which will be on constant display at the Pharmacy exhibit.

The manufacturing houses will have commercial displays on the same floor as the Pharmacy exhibit. The second floor of the Hall of Science Building will be given over to a display of the Basic Sciences.

As an example of the magnitude and importance this exposition will have, it was mentioned as an example of the money being spent, that

Sir Henry Wellcome, of the Burroughs Wellcome & Company, is spending $100,000 on a private display.

A trial opening of the entire exposition has been set for May 15th, and it is assured that the Pharmacy exhibit will be ready by that time.

Miss Esther Barney, who will have charge of the Pharmacy booth, was introduced to the audience.

The meeting was closed with a rising vote of thanks to Mr. Christensen.

LAWRENCE TEMPLETON, *Secretary.*

DETROIT.

The April meeting of the Detroit Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held in the Webster Hall, April 28th; a dinner preceded the meeting. This was the largest student meeting in the history of the Branch. Owing to the absence of Secretary Bernard Bialk, due to recent bereavement in his family, Prof. J. L. Dorion, of Detroit Institute of Technology, acted in his behalf. The meeting was presided over by second vice-president Miss Eugenia Lemke. The minutes of the previous meeting were read and approved.

Miss Lemke then called on Dean Edward H. Kraus, University of Michigan, who referred to the May meeting in Ann Arbor and the second annual Pharmaceutical Conference. He invited all present to attend and make it a success.

Miss Lemke called attention to the fact that several leaders in American Pharmacy were present, among them, the following: President Clare Allan, of National Association of Boards of Pharmacy; Secretary Samuel Henry, of the N. A. R. D.; President Charles Stocking, of American Association of Colleges of Pharmacy; Professor Scoville, author and scholar, and Leonard A. Seltzer.

Mr. Henry gave a short address in which he told the students that in seeking for the proper foundation of pharmacy, not to overlook the building of character, a prime asset in the success of their careers.

The vice-president then called on the following speakers who represented the four Michigan pharmacy schools. The subjects and names of students follow: The Detroit Institute of Technology—Mr. Tyszka, "Wine, History and Use in Medicine;" Mr. Hechtman, "Vitamin A in Haliver Oil;" Mr. Robinson, "New Legislation for Pharmacy."

University of Michigan—Elmon Cataline, "Biography of Dean Prescott of University of Michigan;" Felix Johnston, "Health Service to Students of University of Michigan."

City College—Mr. Freeman, "Pharmacy as a Profession;" Mr. Maliaki, "Emulsions;" Mr. Weiss, "Cost of Medical Care."

Ferris Institute—Clyde Foster, "Value of Arsenic as an Insecticide;" Andrew Zamiara, "Methylene Blue in Medicine."

Synopses of the papers follow: "Value of Arsenic as an Insecticide," by Clyde Foster. "Arsenic has been used for many centuries as a poison in various forms, such as Paris Green, Lead Arsenate, Calcium Arsenate. Over eight million pounds are used annually. Our food supply of vegetables and fruits depends to a great extent on the value of arsenic as an effective insecticide."

"Pharmacy as a Profession," by Mr. Freeman. "The pharmacist plays an important rôle as the friend and helper of the people." He discussed ways and means of improving conditions such as a closer contact and more helpful aid between the employer and the apprentice, the college instructor and the student.

"Biography of Dean Prescott of the University of Michigan Pharmacy Department," Elmon Cataline gave a very interesting life history of Dean Prescott, one of the outstanding leaders of pharmacy; he was beloved and esteemed as a scholar, educator and investigator of American pharmacy.

"Wine, Its History and Use in Medicine," by Mr. Tyszka. This paper proved to be an instructive history of the use of wine in early medicine. He said every nation had its various kinds of wines for various diseases and this persisted even to the present time.

"Emulsions," by Mr. Maliaki. This paper dealt at length with the improvements in bases for emulsions, naming several organic bases such as triphenylamine. He said these bases were more stable and easier to work with and produced better results. He claimed they would, no doubt, lead to a new era in emulsions.

"Health Services to Students at U. of M.," Felix Johnston gave a brief history of the origin of this service. He said the students of the Pharmacy Department manufactured practically all of the preparations used in the department. It provided an efficient system for the medical care of thousands of students at a very reasonable rate per year. At the present time 35 employees are kept busy.

"Vitamin A in Haliver Oil," by Mr. Hecht-

man. The speaker gave the history of vitamin A and discussed the halibut oil as a source of this valuable principle. He said that Haliver oil with viosterol is of such potency that three drops of it are equal in vitamin potency to a teaspoonful of cod liver oil. It is now widely used to provide both the growth-promoting and disease-resisting vitamin A in highly concentrated form.

"Medicinal Uses of Methylene Blue," by Andrew Zamiara. This paper dealt with the history of methylene blue and its various uses as antiperiodic, stain and attenuating agent. He said it had recently been successfully used as an antidote for cyanide poisoning.

"Gospel of the Cost of Medical Care," by Mr. Weiss. He said the outlets of medicine included hospitals, doctors, pharmacies and other outlets, such as department stores. He discussed patent medicines at length. The speaker pointed out that pharmacy always has dominated the sale of medicine.

"Need of Improvement in Pharmacy Laws," by Douglas Robinson. He discussed the subject under four divisions: chain stores, patent medicines, the house to house vendor and the grocery-store druggist. This proved to be a very interesting and timely subject and was very well presented by the speaker.

Miss Lemke complimented Ferris Institute on its first participation in the annual student meeting of the Detroit Section of A. Ph. A., and called upon Clyde Foster of Ferris Institute as first speaker.

The student papers were very well prepared and ably presented. Owing to the large number of speakers, the entire time was given over to them.

Dean R. T. Lakey made a motion that the acting secretary send a letter of condolence to Secretary Bialk—carried unanimously. The student speakers were given a rising vote of thanks. About 200 members and students were present at this meeting.

J. L. Donen, *Acting Secretary.*

UNIVERSITY OF FLORIDA, STUDENT BRANCH.

A special meeting of the University of Florida Student Branch of the American Pharmaceutical Association was called on Wednesday, April 26th, at the Chemistry-Pharmacy building for the purpose of electing officers for next year and to bring up some new business.

The meeting was called to order by President Mallory and a general discussion was held. Several short talks were given by members regarding having some kind of a charm or key for our members and the secretary was asked to write to Secretary E. F. Kelly concerning this matter.

The election of officers resulted as follows: *President,* George R. Jones; *Vice-President,* Milton H. Fulmer; *Secretary,* G. C. Sparks, Jr.; *Treasurer,* R. S. Johnson.

The newly elected officers took office immediately. Another meeting is planned before the end of the semester.

G. C. Sparks, Jr., *Secretary.*

NEW YORK.

The April meeting of the New York Branch of the American Pharmaceutical Association was held at the New York College of Pharmacy, Columbia University, on Monday, April 10th. There were approximately forty members present.

President Bilhuber called upon the secretary for a report of the previous meeting. This was read and accepted.

Chairman Lehman, of the Committee on Legislation and Education, reported that under the Model Narcotic Law a magistrate would have the authority to revoke the license of a pharmacist. This power, he felt, should remain with the Board of Pharmacy, as at present. An important bill known as Copeland S. 526, has been passed which virtually gives the physician unlimited rights in the prescribing of spirituous liquors. Eventually the liquor prescription form will be done away with and ordinary prescription blanks with a special stamp attached will be employed.

Chairman Kidder, of the Professional Relations Committee, next reported that he was making considerable progress in organizing a joint Physician-Pharmacist meeting to be held during the 1933–1934 season. Arrangements have been made to have several prominent physicians speak.

The chairman of the Membership Committee, Dr. Kassner, reported that Messrs. Robert Stauber and Frank Pokorny had applied for membership in the parent organization and would be affiliated with the New York Branch.

Dr. Schaefer reported concerning the activities of his committee in connection with the organization of the Northern New Jersey Branch of the American Pharmaceutical

ASSOCIATION. He read the correspondence and stated that negotiations are under way to avoid conflict of meeting nights. Likewise efforts are being made to permit membership in more than one branch if a member so desires.

Dr. Bilhuber then introduced the speaker for the evening, Dr. Hazel M. Hatfield, Assistant Director in the Bureau of Laboratories, Department of Health, New York City. She discussed certain aspects of the Health Department service. Parts of her address follow:

One of the functions of the New York City Health Department is the production and distribution, through its Bureau of Laboratories, of biological preparations.

The great diversity of operations involved in the preparation of these biological products under the directorship of Dr. William H. Park is carried out largely in the headquarters' Laboratories, New York City; the antitoxins, antiserums and smallpox vaccines, requiring the use of large animals, are prepared at the branch laboratory at Otisville, N. Y.

Products involving the use of only small animals or none at all, as well as the preparation of the toxins and vaccines are prepared at the 16th Street Laboratories.

The distribution of biologicals is carried on under the supervision of the Distribution Department in the 16th Street Laboratory. The means of distribution may be grouped as follows:

(*a*) A duly licensed physician may obtain any of these products by applying at the headquarters of the Bureau of Laboratories. The products may be had free of charge except the smallpox vaccine which must be paid for. (Smallpox vaccinations are done by the Health Department if it is a hardship for the patient to pay. Vaccinations are also carried out in the public schools without charge.)

(*b*) Borough offices are prepared to distribute biologicals.

(*c*) Consignment stations, popularly known as "Board of Health Stations" or "Culture Stations" are located in about 475 drug stores, hospitals and clinics throughout the five boroughs. Druggists are obligated to furnish the more commonly used biological preparations, especially diphtheria antitoxin, and to obtain the others, as requested, from the Research Laboratory.

Varying regulations as to availability and price govern the distribution of the various biologicals from the different distribution points mentioned above.

In general, diphtheria and tetanus antitoxins must be paid for or a free slip made out in lieu of cash. If a syringe is wanted it must always be paid for at a charge of 25 cents.

It has always been a function of the laboratory to conduct research work along lines of more or less immediate practical value from a public health standpoint and, when new laboratory products seem necessary as a preventive or curative measure or promise to possess such value, the manufacture of such products also is sanctioned by the Health Department and may be distributed to duly licensed physicians both within and without the state without charge with a view to the accumulation of clinical data on their use. Eventually they may be added to the items for which a charge is made.

The Health Department operates about 475 so-called culture stations scattered throughout the five boroughs. These are located in drug stores and have been established upon the application of the druggist to operate such a station. The first consideration is to scatter these stations in the section of the boroughs that are already built up. There has been no increase in the appropriation for this work for a number of years, therefore, it is difficult to keep pace with the growth of population into the newer sections of the various boroughs. The druggist maintaining a station is exercising a public health function. In accepting a station after the application has been approved, the druggist is obliged to sign a contract by which he obligates himself to handle biologicals, make a cash accounting to the Health Department Auditor, to hold and distribute laboratory outfits in a manner prescribed, and to accept specimens for examination by the Department: these to be forwarded in the case of a sub-station or held for the collector if the culture station be a collecting one.

Diphtheria culture tubes, Wassermann outfits, etc., represent a large outlay for the Department and are intended only as a means of getting specimens back to the Department laboratory for examination. It is a matter of considerable difficulty to control this output, so that the minimum shall be diverted to other purposes by the physicians. To this end druggists are directed to issue not more than two or three Wassermann's to any one physician at any one time. It is provided, however, that any physician applying directly to the Department or whose name is given to us by the druggist as one who specializes in G. U. work and who, therefore, requires an unusual number of

outfits, may be taken care of by a large package.

Every culture station means that the Department must stock it with biologicals and with Wassermann and other outfits and the greater is the amount of biologicals subject to aging and to eventually becoming outdated, representing a loss to the Department. An increase in the number of stations means a greater demand upon the service because every station must be supervised and restocked, and without a corresponding increase in the personnel, this must inevitably affect the service and results in complaints. For the maximum service to the community, it would be advisable to have a smaller number of stations with a maximum of attention from the Department.

Following Dr. Hatfield's address two of her co-workers, Miss Mishylow and Mr. Greenwald, were called upon to explain the work of the Department in preparing bacterial vaccines, tuberculin, antitoxins and antibacterial serums.

During the discussion, in which Messrs. Schaefer, Seeley, Lascoff and others took part, several additional points of interest were brought out as follows: Most of the products are dispensed without charge at the culture stations. The prices charged by the City for its products are somewhat below the usual price of independent manufacturers.

Following the discussion a rising vote of thanks was given the speakers.

RUDOLF HAUCK, *Secretary.*

PHILADELPHIA.

The April meeting of the Philadelphia Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at the Philadelphia College of Pharmacy and Science, on Tuesday evening, April 18, 1933. The minutes of the preceding meeting were read and approved.

President Eby announced the following committee appointments for 1933–1934:

Committee on Practical Pharmacy: *Chairman,* Adley B. Nichols; John Walton, L. G. Penn.

Committee on Professional Relations: *Chairman,* Dr. H. Everet Kendig; Dr. Wilmer Krusen, W. L. Cliffe.

Committee on Membership: *Chairman,* L. L. Miller; Alfred Barol, G. K. Schacterle, Wm. J. Stoneback, Harvey P. Frank, Robert Schrey, S. P. Hanig.

Committee on Entertainment: *Chairman,* J. W. E. Harrisson; Quintus Hoch, George E. Byers.

An interesting lecture was presented by Dr. Henry Field Smyth, Director of the Laboratory of Hygiene, University of Pennsylvania, and president of the Pennsylvania State Health Association. His topic was "The Pharmacist and Public Health Problems."

Dr. Smyth began with the historical development of public health movements, stating that ancient history shows attempts at provision for public health, in water supplies and sewage disposal. This knowledge became lost and at the end of the 18th century we find, for large communities, no pure water supply, no pure milk supply and no proper sewage disposal.

Interest in community health from the standpoint of sanitation began in the 19th century, when the engineer represented the first public health officer. Gradually the physician, the laboratory technician, the pharmacist and nurses assumed importance in the work, and finally sociologists began investigations of child health and social diseases.

The biological origin of disease was then considered, with the discovery and development of antitoxins, vaccines, etc., and attention was focused on the causative agents of disease.

At the close of the 19th century emphasis was laid on provision for sanitation to the states, with the realization that public health was a purchasable commodity. Here Dr. Smyth stated that $2.50 per capita per year should provide ideal health conditions in a large community. All communities are spending far less than this at present.

The pharmacist should be trained to dispense good advice as well as good drugs, and can assist in public health work by educating the people who enter his pharmacy. He should be ready to dispense intelligently, biologicals, special foods, insecticides, toilet articles of the better grade and other things that affect the health and happiness of the community. His obligation should be to interpret public health to his neighborhood, and to do his part in legislation regarding public health.

An interesting series of charts showing the effect of public health movements in controlling

such diseases as typhoid, diphtheria and tuberculosis enhanced the value of the lecture.

The audience tendered Dr. Smyth a rising vote of appreciation.

E. H. MacLaughlin, *Secretary.*

NORTHWESTERN.

At the joint meeting of the Wulling Club and the Northwestern Branch of the American Pharmaceutical Association held May 12th, in the main lecture room of the College of Pharmacy of the University of Minnesota, the following program was carried out, James Gardner, vice-president of the Wulling Club and Rugnar Almin, president of the Northwestern Branch, presiding jointly:

The Wulling Club Constitution was enlarged by adoption of the following:

"The president and officers shall be elected in the spring quarter of each year, the incoming president to take complete charge of the second meeting of that quarter, and of meetings of the following year, the person elected to have been chosen from the junior class of the College."

Under this addition the president assumes office during the last quarter of his junior year instead of assuming office during the fall quarter of his senior year. The chairman announced the cost of the Wulling Club Key requires an assessment of 10 cents per member. Election of officers resulted as follows: *President,* Milan Booth; *Vice-President,* Curtis Waldon; *Secretary-Treasurer,* Ruth Jaehning: *Representative to the Executive Committee for one year,* Orace Hanson.

Dean Wulling was called upon to give a brief address in behalf of the Northwestern Branch of the American Pharmaceutical Associaton on the aims and purposes of the Association. He urgently invited students to join the Association and the Branch. Continuing the Branch program, the Dean then spoke briefly on "First Aids to the Injured."

The Baltimore Branch of the American Pharmaceutical Association held its May meeting on the 12th. A report will be made in the next issue of the Journal. The speakers of the evening were Dr. S. L. Hilton, whose subject was "Scientific Pharmacy and Prescriptions;" Prof. Marvin J. Andrews of the School of Pharmacy of the University of Maryland spoke on "Errors in Dispensing."

The principal speaker at the May meeting of Philadelphia Branch, A. Ph. A. was Robert L. Swain, president-elect of the American Pharmaceutical Association. The subject of his address was "A Critical View of Present-Day Conditions in Pharmacy."

UNITED STATES CIVIL SERVICE EXAMINATIONS.

The United States Civil Service Commission announces open competitive examinations for Junior Pharmacist and Assistant Pharmaceutic Aide.

Applications for the positions of junior pharmacist and assistant pharmaceutic aide must be on file with the U. S. Civil Service Commission at Washington, D. C., not later than May 23, 1933.

The examinations are to fill vacancies in the United States Veterans' Administration, in the Public Health Service and in positions requiring similar qualifications throughout the United States.

The entrance salary for junior pharmacist is $2000 a year, and for assistant pharmaceutic aide $1620 a year. The salaries named are subject to a deduction of 15 per cent as a measure of economy, and a retirement deduction of $3\frac{1}{2}$ per cent.

Applicants must submit evidence that they are full-licensed pharmacists, such license having been obtained as the result of examination before a state board of pharmacy. Certain specified education and experience are also required.

Full information may be obtained from the Secretary of the United States Civil Service Board of Examiners at the post office or customhouse in any city, or from the United States Civil Service Commission, Washington, D. C.

CONFERENCE ON THE PURE FOOD AND DRUGS ACT.

A conference of the representatives of pharmacy and drug-trade activities was held April 27th, with Dr. W. G. Campbell presiding. The purpose was stated to be for obtaining points relative to the possible revision of the act. An editorial on the subject appears in this issue of the Journal.

EDITORIAL NOTES

Editor: E. G. Eberle, 10 West Chase Street, Baltimore, Md.

Members of the Council, A. PH. A.: S. L. HILTON, *Chairman;* CHARLES H. LAWALL, *Vice-Chairman;* E. F. KELLY, *Secretary;* H. V. ARNY, A. G. DUMEZ, H. A. B. DUNNING, WILLIAM B. DAY, C. E. CASPARI, J. H. BEAL, T. J. BRADLEY, AMBROSE HUNSBERGER. *Ex-Officio Members:* W. BRUCE PHILIP, *President;* ROWLAND JONES, G. H. GROMMET, *Vice-Presidents;* C. W. HOLTON, *Treasurer;* E. G. EBERLE, *Editor of the Journal;* A. G. DUMEZ, *Editor of the Year Book;* J. W. SLOCUM, *Chairman of the House of Delegates.*

Collaborators: The Members of the Council; E. FULLERTON COOK, *Chairman,* U. S. P. Revision Committee; E. N. GATHERCOAL, *Chairman,* N. F. Revision Committee; Chairmen of the Sections, A. PH. A.: W. J. HUSA, W. J. RIVARD, W. PAUL BRIGGS, LEON MONELL, LOUIS GERSHENFELD, CHARLES H. STOCKING, *President,* A. A. C. P.; CHARLES B. JORDAN, *Chairman,* Executive Committee, A. A. C. P.; CLARE F. ALLAN, *President,* N. A. B. P.; HENRY C. CHRISTENSEN, *Secretary,* N. A. B. P. Scientific Section—Board of Review on Papers: *Chairman,* L. W. ROWE, Detroit, Mich.; JOHN C. KRANTZ, JR., Baltimore, Md.; F. J. BACON, Cleveland, Ohio.

The Type Prescriptions on page 368 of the JOURNAL, suggested to physicians, should have been credited to the Academy of Pharmacy, Cleveland, Ohio. This group of pharmacists is doing successful work in acquainting physicians with the United States Pharmacopœia and the National Formulary and thereby encouraging prescription writing.

THE COUNCIL ON MEDICAL EDUCATION.

The Council on Medical Education and Hospitals has been a great influence as a standardizing movement in American higher education. Chancelor Dr. Samuel P. Capen, of the University of Buffalo, delivered an address before the Annual Congress on Medical Education and Licensure at Chicago, from which a few statements are abstracted:

"Colleges of liberal arts have been defined and classified by a variety of bodies having a variety of different, and occasionally conflicting, conceptions of college education. Associations of practitioners or teachers—and sometimes both together—representing law, dentistry, pharmacy, architecture and librarianship have prescribed standards for schools preparing for these professions and enforce the standards through classification and publicity. Bodies representing other professions are already in the early stages of the same procedure. In short, the Council on Medical Education and Hospitals reformed not medical education alone. Through the influence of its example it has brought about the general reform of professional education. And the progress that has been made in the elevation of professional education in other fields is only a little less remarkable than the great upswing in medical education."

The *Journal of the American Medical Association,* commenting on the importance of Licensure states that "doctors, lawyers, pharmacists and members of other professions are licensed in most instances for the protection of the public. Thus the dangers of unskilful ministrations by untrained, and therefore unqualified, persons are in part controlled. *The public takes it for granted that practitioners licensed by the state are reliable and may be consulted with reasonable security.* (Italics ours.) Twenty-one years ago, by a merger of two preexisting groups, the Federation of State Medical Boards of the United States was formed. Its purpose was to bring order out of the chaos then prevailing in medical licensure and to enforce reasonable standards of preliminary and professional education for all who would be legally authorized to practice medicine. Though much has been accomplished, much remains to be done before that goal is obtained."

THE AMERICAN PHARMACY BUILDING.

The Sunday edition of the *Baltimore Sun* describes the changes going on in Washington in the district southwest of the White House. It says, "Unquestionably the handsomest of the replacements is the white marble administration Building of the Public Health Service now practically completed. Not far away is the new Red Cross Office Building. In this neighborhood the Pan-American Union expects to build new office quarters. Next door

to the Academy of Science the A. PH. A. is constructing a marble building to house its organization activities. This will be the first of the monumental buildings along Constitution Avenue to be seen from the Arlington Memorial Bridge. Northwest of it, on the United States Naval Hospital grounds, the steel frame work of the National Institute of Health has been erected.

A CENTURY OF PROGRESS, CHICAGO.

Exhibits, tying up with pharmacy, medicine, surgery, disease prevention and dentistry, will be housed in the Hall of Science. They will be situated around a great circle in the center of which a fountain will play. The story of drugs and medicines, down through the ages, will be told but special stress will be laid on the marvelous advances of the last 100 years.

The AMERICAN PHARMACEUTICAL ASSOCIATION will have a vivid, living display in which will be told the whole history of pharmacy from its crude beginning, steeped in superstition and ignorance, to its scientific to-day.

The American Medical Association will reveal the crude start of the physician's art and carry the story into the days of the saddle-back doctor of early America and on to the motorized doctor of now with his laboratories, hospitals and highly specialized equipment.

The Robert Koch Institute will depict the story of the century of war on tuberculosis revealing how, step by step, this great scourge has been all but conquered. The Milwaukee Museum will offer a display picturing the primitive medicine of the Indians. The aboriginal natives of the Americas have made their gifts to the modern science of drugs—quinine, cascara sagrada and others. The Wellcome Museum, of England, will tell the story of the history of British medicine and surgery; Pasteur Institute the story of Louis Pasteur, who gave to the world proof of the Germ Theory of Disease.

A special feature will be the Transparent Man. This is a life-size model of the human body composed of cellon. Looking upon this the visitor can see the interior workings of the human body as if gifted with X-ray eyes.

Notable anniversaries will be celebrated during the Fair; anniversaries which mean much to the world of medicine and pharmacy.

Reference is made elsewhere to the address of Sir Henry H. Dale, director of the Institute of Medical Research, London. In the picture herewith Sir Henry H. Dale is shown on the left and on the right Josiah K. Lilly and in the center of the group is George W. Merck.

EIGHTIETH BIRTHDAY OF DR. HANS HORST MEYER.

The Berlin correspondent of the *Journal of the American Medical Association* writes: "The recognized leader among German pharmacists, Professor Hans Horst Meyer, of Vienna, celebrated his eightieth birthday, March 17th. At the age of twenty-nine he held the chair of pharmacology at the University of Dorpat, Estonia. From Dorpat he was called to Marburg; in 1904 he was given the chair of pharmacology at Vienna, and, refusing a call to Berlin, he held this position until he reached the age of enforced retirement. On his seventieth birthday, the Vienna Academy of Sciences established the Hans Horst Meyer prize, which is bestowed every five years for the best research in the German language in the field of experimental medicine."—*Science*, May 12th.

Dr. James B. Conant, Sheldon Emery, professor of organic chemistry, was on May 8th elected president of Harvard University by the corporation to succeed Dr. A. Lawrence Lowell.

PERSONAL AND NEWS ITEMS.

THE REMINGTON MEDALIST FOR 1933.

Evander F. Kelly, secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION, has been named Remington medalist for 1933. A sketch of the recipient will have to be deferred until the time of the formal award, for which time and date have not been fixed. It is hardly necessary to point out the qualifications which received consideration in his selection, but a few of them are briefly referred to in the following:

His services in local, state and national association work are well and favorably known and also his constant attention to all matters pertaining to the advancement of pharmacy and alertness regarding its interests; readiness to speak in its behalf and directing the policies and activities of the AMERICAN PHARMACEUTICAL ASSOCIATION.

He has been and is outstanding in the efforts which have given to American pharmacy its Building which is nearing completion in Washington. In this promotion he is constantly watchful of the interests of pharmacy and has brought about a connection of a high order with the Government, the Fine Arts Commission, the Park and Planning Commission, that is most influential in the promotion of pharmacy. The relationship which exists with other organizations of pharmacy and related activities have been upheld and strengthened under his direction and coöperation. Possibly no one has contributed quite as much as he toward the establishment of commissions for pharmacists in the Public Health Service and the change of the rating of pharmacists by the Personal Classification Board. His direction is shown in all efforts for pharmacy and always influential for its advancement. The recognition by the Government "Pharmacy as a Career" in which he had a large part, and his discussions relating to educational and legislative problems, the Food and Drugs Act, etc., evidence his thoughtful consideration, clear presentation and efficient leadership.

The responsibilities assigned to him testify to the value of his services as secretary of the AMERICAN PHARMACEUTICAL ASSOCIATION, National Drug Trade Conference, as member of the Board of Trustees of the U. S. Pharmacopœia, State Board of Health, as chairman of the Council on Pharmaceutical Education; prescription surveys, and other important duties and undertakings, faithfully and successfully performed, speak for the decision reached by the Committee of Award.

A picture of the March-April *Patchwork* shows Dr. James H. Beal exhibiting his collection of shells which constitutes a museum, as it contains about 11,000 specimens gathered from all parts of the world. Dr. Beal took up the subject of shells as a hobby about forty-five years ago and has continued his collection of them since that time. Study is given to every specimen, so there is probably no collection which surpasses this in quality. One must visit this museum to fully appreciate the unique shapes and beautiful coloring.

Dr. George W. McCoy, director of the National Institute of Health of the United States Public Health Service, delivered a public address on April 27th, under the auspices of the Lehigh University Chapter of Sigma Xi, on "Our National Defense against Disease."

Dean Robert C. Wilson, secretary of Georgia Pharmaceutical Association, will be the principal speaker at **South Carolina Pharmaceutical Association,** to be held in Greenville, June 14th and 15th.

Charles H. LaWall has described the collection of ancient pharmaceutical shelfware, mortars, weights, manuscripts and other apparatus of the collection shown on page 373 of this issue of the JOURNAL. This collection will be exhibited at Chicago World's Fair.

John K. Clemmer is candidate for Miami City Commission. He is vice-president of the Florida State Board of Pharmacy, of which he has been a member for five years, having been recently reappointed by Gov. David Sholtz; and chairman of the southeastern district for the National Association of Boards of Pharmacy.

A recent issue of the *Apothecary* speaks of the coöperation which the pharmacists of Massachusetts are giving the Board of Health in distributing literature and otherwise informing the public about the dangers of certain medication. In that way the pharmacy becomes a public health station.

Tile and Till, for May, carries an interesting article on "Indiana's Pioneer Village and Apothecary Shop," by E. Y. Guernsey. It presents an effort to restore a lost village, Spring Mill, which is being reconstructed with strict accord to historic accuracy. The old apothecary shop is shown together with the apothecary, Dr. Joseph Lemon, and his wife.

C. P. Van Schaack, of Chicago, after fifty-four years of active connection with the wholesale drug trade, has retired. He started in business with George H. Schaefer of Ft. Madison, Iowa. Mr. Van Schaack has been an active member of the A. PH. A. for many years.

Dr. John C. Krantz, Jr., has contributed an interesting article to the *Druggists Circular*, running through several issues, entitled "The Changing Order of Modern Therapeutics."

Pharmacist J. Cameron, member of the A. PH. A., in an article on "Pharmacy in China," printed in the *Pharmaceutical Journal*, states that "the Chinese Pharmacopœia is now the official guide. However, it is not in general use and the U. S. Pharmacopœia and the British Pharmacopœia are used to a greater extent." He speaks of a number of pharmacies in various cities of China which are well stocked and under guidance of highly trained pharmacists.

Herbert Skinner, chairman of the British Pharmaceutical Conference, visitor at the Toronto meeting, and honorary member of the AMERICAN PHARMACEUTICAL ASSOCIATION, has contributed "American Pharmaceutical Notes," running through several issues of *The Chemist and Druggist*. The pages of the article in the April 29th number are illustrated by views of the pharmacy of J. Leon Lascoff & Son. The contributor in his lines of comment shows that he has been on this side of the Atlantic before but, perhaps, has not attended previous A. PH. A. meetings. Members of the A. PH. A. are pleased to have visitors of the type at the Toronto meeting who come to acquaint themselves with our ways of doing things and inform us about their own. No doubt, if times were better, there would be more interchange of visitations—they are beneficial to hosts and visitors.

Dr. Frank B. Kirby, former sales manager for Abbott Laboratories, has become its Director of Education, having to do with educating salesmen, contacts with drug and medical groups. Dr. Kirby is also secretary of the Committee on Pharmacy Exhibit, Chicago World's Fair.

OBITUARY.

EDWARD STABLER LEDBEATER.

E. S. Ledbeater, prominent pharmacist of Alexandria, Va., died at his home after an illness of several months. The historic pharmacy of which the deceased had been proprietor was established in 1792 by Mr. Ledbeater's great grandfather, William Stabler. Richard H. Stabler, a relative, was president of the AMERICAN PHARMACEUTICAL ASSOCIATION 1870–1871.

Among the historical records of this pharmacy are entries showing that General George Washington and Martha Washington were patrons of the store and several of the Washingtons were for a time engaged there. General Robert E. Lee was a patron and in this store General J. E. B. Stuart, then courier, delivered an order to him for Colonel Lee to proceed to Harpers Ferry to subdue the John Brown uprising. Until two weeks ago the store had not ceased to function since its establishment.

For the past thirty years Mr. Ledbeater had been superintendent of Christ Church Sunday School and vestryman of the Church.

The deceased had never married and is survived by two sisters, Mrs. William B. Lloyd and Mrs. Laurence Stabler and a brother, Clarence C. Stabler.

WILLIAM H. MARTINDALE.

William Harrison Martindale, well and favorably known British pharmacist and author, died at his home in London, April 8th, aged fifty-eight years. He was the son of William Martindale, former president of the British Pharmaceutical Society and of the British Pharmaceutical Conference. He was educated at the University College, London, and at the University of Marburg, and on the death of his father continued the business established by him. He also revised the later editions of "The Extra Pharmacopœia" and contributed largely to pharmaceutical literature. His monographs included "Notes on Radio-activity," "Pharmacy Notes from Various Parts of the World," and some of his medical writings were prepared in conjunction with Dr. J. Graham Willmore—"Treatment of Amœbic Dysentary," etc. However, he is best known to American pharmacists by "The Extra Pharmacopœia."

C. Edward Sage, in the *Pharmaceutical*

Journal and Pharmacist, states that "with the passing of W. H. Martindale we have counted off another epoch in the history of English pharmacy. His father's lifetime work furnished him, in 1902, with an inheritance of tradition and scientific achievement such as few men start with, and he accepted it as a trust, and honorably and faithfully pursued his profession in the endeavor to add to the armory by which medicine fights disease. Martindale's student days were passed in the period when bacteriology and radiology were novelties to the medical profession, yet he took pains to add those sciences to his equipment, knowing quite well that pharmacy would have to take its share in rendering their benefits available for medical practice."

AUGUST DIEHL.

August Diehl was born at or near Easton, Pennsylvania, on January 6, 1869. After leaving public school in that city, he worked as a boy in a drug store, until his folks moved to New York, when he was about sixteen years old. He entered the New York College of Pharmacy in 1886, graduating in the famous Blizzard Class of 1888. In 1900 he took over both of Schleussner's Bedford Ave. stores, having entered into partnership with his brother Theodore. The latter died about twenty years ago, and the Taylor St. store was sold, while the Penn St. store was his property until the end. He was never married.

He was a member of the AMERICAN PHARMACEUTICAL ASSOCIATION, of the New York Veteran Druggists' Association, Kings County, German Apothecaries' Association, Williamsburg Druggists' Association, etc. He was a director of the New York Consolidated Drug Co. for about fifteen years, having served as president of that corporation for seven years.

Mr. Diehl was a quiet, lovable and somewhat bashful sort of an individual, but a very capable pharmacist. His death ensued as a result of an attack of pneumonia on January 14, 1933.—*Courtesy William C. Anderson and Robert Lehman.*

LAWSON C. COULSON.

Lawson C. Coulson, of Corsicana, well-known Texas druggist, died at his home Sunday, March 12th, after a ten-day illness with pneumonia. He is survived by his wife, one son, three daughters and two brothers, Tom Coulson of Dallas, and Will Coulson of Coleman. Mr. Coulson was born and reared in Corsicana, and was a leader in civic, social and business circles for many years. He entered the drug business with his brother, Tom Coulson, now of Dallas, later becoming proprietor of the business and it was only recently that he retired.

THOMAS J. KEENAN.

Thomas J. Keenan, chemist and technical journalist, died May 1st, in his home in South Orange, N. J., aged sixty-seven years.

Mr. Keenan was born in Dundee, Scotland, August 29, 1866, and studied chemistry and pharmacy there. He came to New York and until 1892 was employed as a hospital pharmacist. In that year he joined the editorial staff of the *Pharmaceutical Record* and was editor of the publication when, in 1903, it was consolidated with the *American Druggist*. He was associate editor of the latter publication until 1911, when he became editor of *Paper*. He was one of the organizers of the Technical Association of the Pulp and Paper Industry and served as its secretary-treasurer from 1915 to 1920.

In 1923, Mr. Keenan became editor of scientific publications for Lehn & Fink, Inc. About a year later, he became associate editor of *The Paper Industry* and remained in that position until late in 1932. His wife died about that time, and Mr. Keenan went to Scotland. He returned several months ago and had since been devoting himself to free-lance journalist work and the writing of technical articles.

DR. HIKOEMON KIMURA.

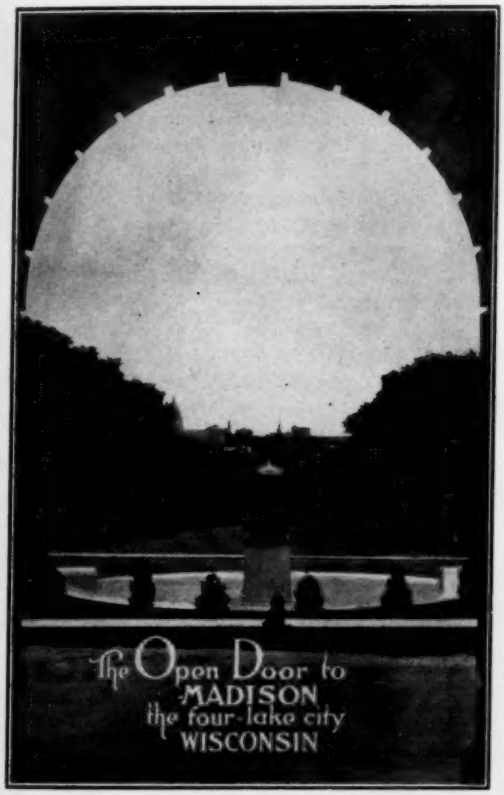
The death of Dr. Hikoemon Kimura, one of the foremost pharmacists of Japan, has been announced. He died on March 31st, aged fifty years. He entered Osaka Kyoritsu Pharmaceutical School in 1895, and graduated in 1897. He joined the army as a pharmacist in 1899, and took a special course in pharmacy at Tokyo Imperial University. In 1902 he became a pharmacist sub-lieutenant and went to the front as a health officer in the Russian-Japanese War. In 1906 he was promoted to pharmacist-lieutenant and then studied pharmacy under Dr. Thoms in Berlin University, 1907 to 1913. He received the degree of Doctor of Pharmacy in 1913 and became Professor of Pharmacy at Osaka Pharmaceutical College. He was president of the Osaka Pharmaceutical College from 1922 to 1925, and

vice-president of the Japan Pharmacists' Union from 1929 to 1931.

MISS CARRIE RITTER.

Miss Carrie Ritter, member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1922, died February 28th, aged 43 years. In 1915 she graduated from the Cincinnati College of Pharmacy and, in the following year, she engaged as pharmacist in the City Hospital of Springfield, Ohio, where also during later years she was X-ray technician. The value of her services are best expressed by the fact that she continued in this service for seventeen years, until the time of her death. We are indebted to her sister, Mrs. Madeline R. Plogstedt, for the foregoing data.

SOCIETIES AND COLLEGES.



View taken from entrance of Bascom Hall, U. of W., looking over Lincoln Terrace. State Capitol Building in distance.

SECTION ON EDUCATION AND LEGISLATION.

The Section on Education and Legislation invites contributions of papers relating to legislation and education. Lengthy papers should be accompanied by abstracts and titles submitted as early as possible so that they can be listed in the program and mimeographed prior to the convention. The chairman of the Section is W. H. Rivard, 10 Beaufort Street, Providence, R. I., and the secretary should be addressed: Charles W. Ballard, 115 W. 68th St., New York, N. Y.

Dean C. E. Mollett is sending out requests for papers and topics for discussion which will be used at a joint meeting of representatives of the Conference of Pharmacognosy and Pharmacology at the meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION at Madison, Wis., in August. Dean Mollett is secretary of the former organization. The object of the conference is to improve the various courses of instruction in schools which are members of the American Association of Colleges of Pharmacy.

AMERICAN DRUG MANUFACTURERS' ASSOCIATION.*

Federal legislative programs, particularly those directed to the revision of the food and drugs act and the control of industrial practices, were outstanding as topics of interest in the twenty-second annual meeting of the American Drug Manufacturers' Association, which completed four days' sessions at Hot Springs, Va., May 11th. Plans to stabilize and improve the drug industry, plans originated by the industry, were also the subject of serious discussion.

Among the matters of more individual interests to members of the association, which came up for discussion, were the patenting of drug and chemical products, the compulsory registration of trade names, and the problems attending insurance, particularly insurance against liability for mishaps alleged to result from the use of drug products. Foreign trade conditions were reviewed and generally were

* From *Oil, Paint and Drug Reporter*, May 15, 1933.

regarded to be favorable. Transportation developments were covered with much informative data. Sales and advertising problems were discussed at the final session. Particular attention was given to the training of salesmen and the proper calculation of sales costs.

The meeting was the most largely attended that the association has held. One hundred seventy-nine persons were here in the convention party, and the official registration was thirty-five in excess of that last year, which had been the high record.

In recognition of the long and able service as treasurer of Franklin Black, who asked to be relieved of the duties of office, the convention made him an honorary, permanent member of the advisory council.

THE NEW OFFICERS.

By unanimous approval of the recommendations of the nominating committee, the association elected the following officers: *President*, A. Homer Smith, Philadelphia; *First Vice-President*, Oscar W. Smith, Detroit; *Second Vice-President*, A. C. Boylston, St. Louis; *Third Vice-President*, John F. Anderson, New Brunswick, N. J.; *Treasurer*, S. DeWitt Clough, Chicago, Ill.

Carson P. Frailey, Albee Building, Washington, was continued by the executive committee as executive vice-president and secretary; Horace W. Bigelow, Detroit, was continued as general counsel.

The following were elected as members of the executive committee: J. H. Foy, Newark, N. J. (reëlected); Willard Ohliger, Detroit (reëlected); and L. N. Upjohn, Kalamazoo, Mich. Nicholas H. Noyes, Indianapolis, as retiring president, automatically became a member of the executive committee, succeeding S. Barksdale Penick, New York, who as the next preceding former president became a member of the advisory council. Other members of the council are two former presidents, Charles J. Lynn, Indianapolis, and Charles G. Merrell, Cincinnati.

Franklin Black, of Charles Pfizer & Co., New York, who retired as treasurer, was elected an honorary member of the advisory council.

BIG PLANS UNDER WAY FOR MISSISSIPPI GOLDEN JUBILEE CONVENTION.

Dates for the Golden Jubilee Convention of the Mississippi State Pharmaceutical Association were set for June 19th, 20th and 21st, by members of the Executive Committee of the organization. The meeting, as previously announced, will be held in Jackson and all plans formulated are being pointed toward one of the largest and most important drug meetings ever held in Mississippi.

OFFICERS OF KANSAS PHARMACEUTICAL ASSOCIATION.

The fifty-fourth annual meeting of the Kansas Pharmaceutical Association was held at Topeka, April 11th, 12th and 13th. The following officers were elected: *President*, Joe Demain, Macksville; *First Vice-President*, C. W. Evans-Lombe, Coffeyville; *Second Vice-President*, Grover Clarkson, Greensburg; *Treasurer*, Walter Varnum, Lawrence; *Librarian*, Dean L. D. Havenhill, of Kansas University. For eligibility to appointment to State Board of Pharmacy, Mac Childs, El Dorado; Joe Paradowsky, Kansas City; J. N. Mulligan, Topeka; Frank Milne, Pratt; Walter Varnum, Lawrence; Kelsey Petro, Topeka; Otto Kuether, Herington; Eugene Cook, Iola; J. E. Youngsberg, Ottawa; Paul Schulz, Beloit; W. C. Laugherty, Syracuse; Warren Morris, Olathe; Terry Foltz, Hutchinson; Charles States, Dodge City; C. W. Evans-Lombe, Coffeyville; Ellis Cookson, Wichita; E. I. Fish, Sedan; C. M. McCaughan, El Dorado; Claude Barricklow, Great Bend.

OFFICERS-ELECT OF THE MINNESOTA STATE PHARMACEUTICAL ASSOCIATION.

The result of the recent election of officers of the Minnesota State Pharmaceutical Association for 1934, conducted by mail, is reported as follows: *President*, Theodore A. Arneson, Montevideo; *First Vice-President*, K. K. Keller, Minneapolis; *Second Vice-President*, Roy G. Paulson, Fairmount; *Third Vice-President*, Evelyn Williams, Minneapolis; *Secretary*, Gustav Bachman, Minneapolis; *Treasurer*, C. T. Heller, Jr., St. Paul; *Executive Committee Member*, C. A. Anderson, Litchfield.

The members recommended for the State Board of Pharmacy are: Hugo O. Peterson, Minneapolis; N. Vere Sanders, Albert Lea; Joseph Vadheim, Tyler; F. W. Moudry, St. Paul; H. O. Tiegen, Moorhead. The governor may appoint one of the above nominees to

serve on the Board of Pharmacy beginning with January 1, 1934, for a term of five years.

NEW YORK PHARMACISTS TO DINE PHYSICIANS.

Dr. J. Leon Lascoff, chairman of the State Committee on U. S. P. and N. F. Propaganda, announces that a meeting will be staged shortly under the joint auspices of the New York Pharmaceutical Conference, the State Association and the New York Academy of Pharmacy in the interests of U. S. P. and N. F. propaganda. It is planned to ask as many pharmacists as are interested to invite one or two physicians each to a supper meeting, at which will be discussed the proper relationship that should exist between the pharmaceutical and medical professions.

MINNESOTA PIONEER DRUG EXHIBIT.

The Minnesota State Historical Society has formulated plans for the establishment of a special collection dealing with the history of Minnesota Pharmacy. The proposed collection will include not only instruments used in the pioneer drug business but also such important manuscript records as pharmacy books, formulas and the business papers of early pharmacists. The Society also hopes to create an exhibit depicting a pioneer drug store. The Historical Society will welcome information about the existence of pharmacy material.

ASSOCIATION NOTES.

The 51st annual meeting of **Lousiana Pharmaceutical Association** was held in Monroe, May 9th and 10th.

Georgia Pharmaceutical Association met in 58th annual convention in Augusta, May 23rd and 24th. Among the speakers were President John A. Goode, of the N. A. R. D.; W. S. Elkin, Jr., Chief Drug Inspector; M. H. Doss, Florida Drug Inspector; Sam Williams, Alabama Pharmaceutical Association; Ed Oslin, Arkansas Pharmaceutical Association.

Maryland and **Delaware** will fraternize, holding their annual meeting at Ocean City, Maryland, June 20th to 22nd.

Kentucky Pharmaceutical Association will meet at Crab Orchard, June 20th–24th. The Entertainment Committee has offered a number of prizes, among them 3 copies of the "A. PH. A. Recipe Book," setting a good example for other associations to give prizes which are of constant value in the drug store.

Chairman Samuel S. Dworkin, of the Committee on Fair Trade, has issued a letter and questionnaire to the members of New York Pharmaceutical Association. The object of the questionnaire is to get the viewpoint of the heads of these firms on some of the outstanding problems confronting the pharmaceutical industry. Among the subjects taken up in the survey are socialization of medicine, dentistry and pharmacy, price maintenance legislation, proprietary advertising, selective distribution, combination sales and free goods.

The result of this study will be tabulated and presented at the coming state meeting.

Dr. W. J. Danforth, Fort Worth, was recently elected District Governor of the Lions Clubs of Texas. He is an active member of the AMERICAN PHARMACEUTICAL ASSOCIATION and interested in civic work. Pharmacists L. O. Donald and D. B. Blaine, of Dallas, Tex., are among those featured in the *Dallas News* as "Builders of Dallas."

Governor Ferguson, of Texas, announced the appointment of Henry F. Hein of San Antonio, AMERICAN PHARMACEUTICAL ASSOCIATION member, as a member of the State Board of Health to succeed J. M. Spoonts of Wichita Falls; and Dan Allen of Ft. Worth, and E. E. Weaver of Houston as members of the Board of Pharmacy to succeed R. R. Townsend of Lamesa, and Frank A. Walter of San Antonio. The list of pharmacists on state boards of health is growing. Mr. Hein is a former president of Texas Pharmaceutical Association and a graduate of the University of Maryland.

F. H. Harris, Chief Pharmacist Mate of the "Tucker," cared for the survivors of the "Akron."

Petty's Pharmacy, in Newark, N. J., has filled its 2,500,000th prescription. This record has been reached in fifty years and is a phenomenal accomplishment.

NEW MEXICO PHARMACEUTICAL ASSOCIATION.

New Mexico pharmacists met in annual convention at Carlsbad during the week of May 22nd. The special scenic feature which will no doubt prove to be the deciding factor as to going or not going is the Carlsbad Caverns, which though only partially explored have been proved to be the most extensive of any known to the world, and many scientists and sightseers have traveled thousands of miles to view

the wonderful stalactite and stalagmite formations and to study their rate of growth, thus fixing their beginning far back in prehistoric times. However, the officers did not depend upon Nature and her wondrous works to attract and justify a large attendance, but formulated one of the best business programs that has ever been put on at a New Mexico meeting—a program which provided food for thought for every one, whether his interest lies in professional pharmacy or in merchandising.

TEXAS PHARMACEUTICAL ASSOCIATION.

Texas Pharmaceutical Association met in Galveston, May 15th–18th. The *Texas Druggist* refers to the history of Galveston in the following:

"Around the colorful character of Jean Lafitte, known as a sort of gentleman privateer, who sailed his five ships into the natural harbor of Galveston in the early part of May 1918, has been woven many romantic tales of adventure. Some refer to him as a pirate bold, yet others deny that he did other than operate on an authorization from three governments who were at war with Spain, to prey upon her commerce in the Caribbean. Undoubtedly he was a loyal patriot, for he took up arms for the United States, stoutly defending his adopted land against England.

"Many are the legends of 'buried treasure' and from this source has sprung the term 'Treasure Island.' But in these later days it has been found that the term is particularly applicable to Galveston for reasons quite apart from buried gold. Galveston's delightful year-around climate, her 32 miles of peerless beach—surf bathing, fishing, hunting and world-wide shipping—make her an island of Treasure indeed."

President L. C. Brenner and Secretary-Treasurer Walter D. Adams have had their reports printed for distribution during the meeting.

Editor Herbert Mayes of the *American Druggist* was one of the principal speakers of the convention.

MASSACHUSETTS COLLEGE OF PHARMACY HISTORICAL SKETCH.

The *Bulletin* of the Massachusetts College of Pharmacy has published a most interesting historical sketch of early pharmacists and pharmacies; a few paragraphs are quoted in the following:

"The first pharmacist mentioned in the public records of Boston was Giles Firmin, Senior, an apothecary from Sudbury, England, who came over in 1633 in the same ship with the Rev. John Cotton. In 1634 Mr. Firmin was a deacon and a selectman.

"The first drug store mentioned was that of William Davis in 1646, on Washington Street: the town pump was set up near it just north of the head of State Street in 1650. He was a man of large fortune for those days, and resided on the north side of State Street, midway between Kilby and Congress Streets. He was Captain of the Ancient and Honorable Artillery Company from 1664 to 1672, and was a representative to the General Court.

"In 1686 John Dutton commended Dr. Benjamin Bullivant, the Apothecary-General, as the most complete Pharmacopœian, not only of Boston, but in all New England. Dr. William Douglas wrote, on December 20, 1721, that there were fourteen apothecary shops in the town. Then, after the English custom, all practitioners dispensed their own medicines, and they continued to do so as long as the town remained under British rule. The first pharmaceutical publication was a tract issued in 1732, *Electuarium novum Alexipharmacum*, by the Rev. Thomas Harward."

GUEST NIGHT AT THE CONNECTICUT COLLEGE OF PHARMACY.

The Second Annual Guest Night, held at the Connecticut College of Pharmacy, New Haven, on Friday evening, April 28th, was a greater success than the initial attempt of last year when over 500 people visited the College. Fair weather favored a large attendance at this annual event which had received wide publicity during the past few weeks. The guest register, inaugurated Friday night, already contains hundreds of signatures but owing to the congestion in the office, many visitors were unable to sign. Among those present were physicians, nurses, students from the Yale Medical School and other departments of the University, pharmacists and people from many other walks of life.

The purpose of Guest Night is to inform the public upon the training of pharmacists and the preparation and testing of medicinal substances. This task, the College believes, is as

much a part of its duties as is the teaching of courses. Toward this end the attempt lived up to its purpose both in the nature of the demonstrations and in the eagerness with which the students were ready to explain their work to the visitors.

All phases of pharmacy activities were shown and greatly interested the visitors.

LEGAL AND LEGISLATIVE.

FOOD AND DRUGS LAW PROPOSALS.

"A proposed draft revising the present Food and Drugs Act was completed May 16th and submitted to the Department of Justice for review," it was announced by Assistant Secretary of Agriculture, R. G. Tugwell.

"The most important provision in the proposed draft is the expansion of the Act to include cosmetics and to regulate advertising of foods, drugs and cosmetics. The new draft does not propose censorship of advertising in advance of its use. However, under its provisions false advertising may be penalized by prosecution in the Federal courts. Prosecution for false advertising will be directed against the source rather than against the medium in which it appears. This will put the responsibility for truthful advertising squarely upon the manufacturer, distributor or dealer. The truth or falsity of advertising will be measured essentially by the same standards as those employed to determine the truth or falsity of label statements.

"The Federal Food and Drugs Act, in its present form, requires a label declaration only for a few narcotics or other drugs. These are: Alcohol, morphine, opium, cocaine, heroine, alpha or beta eucaine, chloroform, cannabis indica, chloral hydrate, acetanilid, or any derivative or preparation of any such substance. 'This requirement unquestionably,' says Dr. Cullen, 'affords the public some protection. But there is a real need for additional safeguards which could be achieved by amending the law so as to insist that additional habit-forming or otherwise dangerous drugs, such as cinchophen, be declared upon the label of medicines in which they are present. Many preparations containing cinchophen—which should never be used without medical supervision—are labeled so as to meet the present requirements of the pure food and drug law.'

"We have noted few cinchophen-bearing preparations which were labeled with remedial claims for arthritis or neuritis," Dr. Cullen declares. "But we have seen a number of such preparations advertised with curative claims for arthritis, neuritis, neuralgia, etc. Such advertising appears in newspapers and radio broadcasts. A medicine containing such a potentially dangerous substance should be used only under the care of a physician. This applies equally to many other patent and proprietary preparations which contain other inherently injurious drugs."

REGULATIONS CONCERNING THE MEDICINAL USE OF LIQUOR.

It is assumed that all pharmacists have studied the regulations applying to the dispensing of Medicinal Liquors. Section 4 of the law includes a number of U. S. P. and N. F. preparations. Section 17 provides that "A pharmacist employed by any person other than a retail druggist may not fill a prescription for spirituous or vinous liquor. A prescription for spirituous or vinous liquor written in accordance with these regulations may not be filed after midnight of the seventh day following the date of its issuance. A pharmacist filing a prescription for spirituous or vinous liquor shall at the time endorse upon said prescription over his own signature in ink or indelible pencil the word 'Canceled' together with the date when the liquor is delivered. The canceled prescriptions must be kept in a separate file as a permanent record available for inspection by properly qualified officers of the Bureau of Industrial Alcohol, or the Bureau of Prohibition at any reasonable hour. No such prescription shall be refilled."

CALIFORNIA PHARMACY LAW.

The *American Pharmacist*, commenting on the redraft of the California Pharmacy Law, says:

"This redraft is a long and important step forward in the better administration of the Pharmacy Law for the protection of the public and to eliminate the abuses in pharmacy resulting from illegal operation of stores. While this redraft does not contain all the remedies and measures which should be incorporated in the law, it does contain those which are feasible and proper at the present time and can probably be enacted without too much diffi-

culty to protect the store owner by cutting down cut-throat competition by men who violate the law. It extends the powers of the Board to assure this, and gives the Board and the State of California the means whereby it can weed out those persons unfit to practice pharmacy and whose presence is a detriment to the state. The present redraft is a reasonable enactment designed to protect all those concerned, the pharmacist himself, the store owner, the Board of Pharmacy and last but not least, the Public."

A bill has passed the California assembly, proposing to penalize any person who by radio or any other broadcasting means asserts any fact, concerning the cure of any ailment by the use of any drug or therapeutic treatment, which is known by him to be untrue and is made with the intention of misleading.

USE OF REAL NAME ON STORE ASKED IN BILL.

A bill re the "foreign" merchant passed through the New York legislature during the closing hours and is now in the hands of the Governor for approval. It is the Schanzer bill amending the penal law by requiring ownership of merchandising establishments to be publicly displayed in the English language upon the window of the establishment or upon a sign.

The bill provides that the person, partnership, association or corporation owning or conducting any shop, store or other establishment wherein the sale of merchandise at retail or wholesale is carried on, shall cause the true, full or legally registered trade name or names of the proprietor or owner or proprietors or owners of such shop, store or other establishment to be publicly revealed and prominently and legibly displayed in the English language either upon a window of such shop or upon a sign conspicuously placed upon the exterior of the building containing the same.

Violation is made a misdemeanor. The act, if approved by the Governor, would take effect September 1st.—*Druggists Circular.*

MALLINCKRODT CHEMICAL WORKS WIN SUIT.

Mallinckrodt Chemical Works have won their suit to the right of U. S. Patent number 1,370,865 which is a patent for the mechanical enclosure of ether cans without the use of solder. The suit was brought in the First District Court of the U. S. for the western division of the Western District of Missouri. The defendants were E. R. Squibb & Sons.

CENTRAL NARCOTICS INTELLIGENCE BUREAU REPORT.

The report for 1932 of the Central Narcotics Intelligence Bureau—the director of which is Russell Pasha—is a book of 170 pages. The Director states that the year 1932 was a more than usual fruitful one for the Bureau and the detective departments of the various governments with which it coöperates. Every phase of habituation and illicit narcotic traffic is reported on. Among the important results of its work is represented by the discontinuance of much of this traffic by concerns that were shipping tons of narcotics, and whose turnover ran into millions of pounds. The report is complete and evidences thoroughness in the effort to stop the illicit use of narcotics.

ARGENTINA DRUG STORE CHAINS.

Under a recent governmental decree drug stores in Argentina cannot be operated by a corporation, according to a report to the U. S. commerce department's regional division from Assistant Trade Commissioner Jule B. Smith, Buenos Aires. The decree, as handed down by the national department of hygiene, follows:

Article 1.—The formation of corporations for the development of pharmacies is declared contrary to law.

Article 2.—The national department of hygiene is hereby recommended to study law now in force together with practical results obtained and before May 1, 1933, present a project which, while guaranteeing public health, will at the same time give thought to the method of operation considered most suitable to the general interests and the exercise of the pharmaceutical professions.

Article 3.—Let the present decree be incorporated in the Regulations of Law No. 4687 and be inserted in the National Register.

The annual joint meeting of the Baltimore and Washington Veteran Druggists' Association was held May 17th, at Olney Inn. Officers of the two organizations presided. President A. C. Taylor and Secretary A. G. DuMez made arrangements for the luncheon and ladies from the two cities graced the occasion. Brief talks were made and the enjoyment of the event was enhanced by fraternizing and a delightful outing.

BOOK NOTICES AND REVIEWS.

Éléments de Pharmacodynamie Spéciale. By EDGAR ZUNZ. 2 volumes. Editors, Masson & Cie. Paris, 1932. Price, 190 francs.

Éléments de Pharmacodynamie Spéciale consists of two octavo volumes, comprising 1272 pages, 167 figures and 181 tables, and is a sequel to a previous publication entitled, *Éléments de Pharmacodynamie Générale.* The three volumes together comprise what is probably the most pretentious and valuable work on general and special pharmacology in the French language. The author, not a Frenchman but a Belgian, has been professor of pharmacology at the University of Brussels for many years and is regarded as one of the outstanding pharmacologists of Europe.

The work is unique in several respects. The method of classification of various drugs is partly chemical, partly physiological and partly clinical and therapeutic, the author's primary object having been to produce a reference handbook which would be most useful for the rational therapeutist as well as for the specialist in pharmacology. The method of treatment is for the most part that which is employed in the latest texts on pharmacology and consists of a brief historical résumé of the particular medicament under discussion followed by a description of its chemical properties, methods of preparation, etc., and a detailed pharmacodynamic analysis of its effects on various physiological functions, the article concluding with a discussion of therapeutic applications of the drug.

There are thirty-three chapters in all. A brief introduction is given in chapter one. To the second chapter are assigned the narcotics of the fatty acid series, including alcohols, general anesthetics, hypnotics and various theories concerning their narcosis. Chapter three is devoted to local anesthetics. Chapter four deals with opium and related compounds. Then follow two chapters setting forth what the author calls "Modifiers of Reflexes," bromides, valerian, etc., on the one hand, and paralyzants of the higher central nervous system, aconitin, delphinium, veratrum, etc., on the other. Chapter seven is devoted to tropines, scopolines and related drugs. Chapter eight deals with ergot and yohimbine. Nicotine and related alkaloids are discussed in chapter nine. The tenth chapter is devoted to apocodeine and the eleventh to curare and curare-like bodies. Strychnine and excitors of the spinal cord are described in chapter twelve. Pilocarpine, physostigmine and choline are discussed in chapter thirteen; adrenaline is treated in chapter fourteen; antipyretics in chapter fifteen; salicylates in chapter sixteen; and heart drugs in chapter seventeen. Chapter eighteen is devoted entirely to vasoconstrictors other than adrenaline while chapter nineteen deals with various vasodilators, including histamine. Diuretics are described in chapter twenty. Chapter twenty-one, comprising about forty pages, deals with internal secretions of the thyroid, parathyroid, suprarenal, male and female sex organs, hypophysis and insulin. A separate chapter is then devoted to other hypoglycemic substances. Chapter twenty-three deals with alkaline metals and earths. Chapter twenty-four, entitled, "Modifiers of Nutrition," contains a study of arsenicals, phosphorus, vanadium, colchicum, iodine and iodides, and vitamins. Chapter twenty-five is assigned to drugs affecting the blood and discusses iron, manganese, chlorophyll, benzene, nucleotides, thorium and mesothorium, X-rays and radium, sodium citrate, oxalates, fluorides, etc. Chapter twenty-six, one hundred pages long, contains an excellent description of the action of drugs upon the gastrointestinal tract from both the purely pharmacodynamic and the therapeutic points of view. Chapter twenty-seven, dealing with action of drugs on the respiratory system, is divided into five sections on (1) excitors and (2) depressors of the respiratory center, (3) expectorants, (4) modifiers of bronchial secretion and (5) antiasthmatics. The twenty-eighth chapter of this work is not only novel but also extremely useful from the standpoint of practical therapeutics. It is entitled, "Medicaments Acting Chiefly on the Skin," and describes a large number of drugs which are used in dermatological practice. This list includes not only caustics, counterirritants and parasiticides but also dyes and thallium. Chapter twenty-nine contains an exposé of various anthelmintics and vermifuges. In the thirtieth chapter more than one hundred pages are devoted to antiseptics and disinfectants. Since it gives complete information on practically every antiseptic known at present, this chapter is one of the most valuable in the whole work. The subject is divided into sections on (1) surgical antiseptics, (2) skin antiseptics, (3) intestinal antiseptics, (4) pulmonary antiseptics, (5) genito-urinary antiseptics and (6) disinfectants. Chapter thirty-one is devoted

to chemotherapy. Here we find a discussion not only of quinine and arsphenamine but also of the newer bismuth preparations, the various dyes which are employed for chemotherapeutic purposes and a study of antimonials, agents employed for antidysentery, gold compounds for intravenous use, chaulmoogra oil and esters, etc. The last two chapters are assigned to vaccines and non-specific protein therapy.

The work is up-to-date and contains a description of some of the latest drugs. Thus, for instance, under cardiac drugs we read of hexeton, cardiazol and coramin. Again, we find detailed accounts of avertin, amytal, uroselectan and other recent developments of pharmaceutical chemistry. There is a detailed description of the pharmacology of benzyl benzoate and of the benzyl esters as well as of benzyl alcohol and of some of its derivatives. Among the newer antiseptics, a section is devoted to mercurochrome although the author lays too much emphasis perhaps on the use of this drug as a chemotherapeutic agent for intravenous injection.

As is the case with almost every reference handbook, a number of errors of omission and commission may be noted in these volumes. Thus, for instance, the section dealing with carbolic acid poisoning is inadequate especially in regard to the latest methods of treatment in such cases. Again, we are surprised at the omission of Barger's name in connection with the chemistry of ergot and likewise with that of W. H. Howell in connection with heparin. The chapter on antipyretics is not very satisfactory. On the other hand, the author gives an unusual amount of space to the discussion of sparteine, a drug little used in the United States.

A valuable feature of Professor Zunz's work are the numerous tables and graphs scattered through its pages. An extensive bibliography is appended to each chapter. In this connection, we cannot refrain from remarking that many names familiar to Americans are not found in the bibliographies, while numerous other authors, more or less unknown to us, are cited. This, of course, is one of the invaluable advantages to be derived from the reading of foreign texts in scientific literature of any kind. A study of such works gives the student a more correct perspective of the subject as a whole. The scientific literature of any nation, while claiming to be impartial and to recognize no distinction of race, creed or color, is very often tinted by the personal predilections of the powers that be in the higher educational institutions of that country. To use an expression of Dr. E. J. Dingwall, a psychologist, "This gives rise to a new witchcraft. The scientific manner of thinking is forgotten and the student is liable to accept conclusions because they are advocated by some person of prominence," or by some coterie of men who have arrogated to themselves the power of passing judgment on the works and productions of other non-political investigators. The monumental work of Professor Zunz will probably not meet with the unqualified approval of the Council on Pharmacy and Chemistry of the American Medical Association. Furthermore, as we glance over some of the more important chapters of these volumes, such as those on adrenaline, insulin, pituitary, opium alkaloids and heart drugs, for instance, we are surprised to find that credit for the fundamental discoveries on those subjects is not preëmpted even to a moderate degree by those exalted American pharmacologists whose names are usually quoted in this connection.

Because of the author's race, this important treatise will probably be relegated to the *Index Purgatorius* of the Nazis, or even consigned to the *auto da fé*, but in the opinion of the reviewer the *Éléments de Pharmacodynamie Spéciale* of Professor Zunz should be classed with the most invaluable reference books on the subject of pharmacology.—DAVID I. MACHT.

The Pharmaceutical Syllabus. Outlining the Course of Instruction for the Degree of Bachelor of Science in Pharmacy (B.S.Phar.) 4th edition. Prepared and published by the National Syllabus Committee, representing the AMERICAN PHARMACEUTICAL ASSOCIATION, the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy. The chairman is J. G. Beard; the Executive Committee is composed of R. A. Lyman, T. J. Bradley and A. L. I. Winne. The Sub-Committee chairmen are: *Materia Medica*, H. M. Burlage; *Chemistry*, Glenn L. Jenkins; *Pharmacy*, E. Fullerton Cook; *Cultural and Basic Subjects*, R. P. Fischelis.

The *Historical Introduction* is complete and gives the organization of the several revisions. The Preface to the 4th edition states that "the Pharmaceutical Syllabus is intended to indicate the subject matter that schools of pharmacy may profitably teach and to set forth that

portion of the subject matter which should be required and that portion which may be looked upon as optional, as well as to indicate the minimum amount of time that should be spent in presenting such material to students. The Syllabus is intended as a guide to state board examiners in that it indicates the nature and extent of professional and applied knowledge that may have been included in the training of the graduate in pharmacy." The Syllabus, therefore, is of value to the members of faculties, board members and students.

The names of those who, in addition to the Committee, shared in the revision of the Syllabus are given and appreciation is expressed for their services.

The sections are represented in Professional and Allied Subjects, Basic Subjects and State Board Examinations and every subject is classified as Required or Optional and a statement is made which sets forth the minimum number of clock hours necessary for its proper presentation. The schedule is of value in giving information regarding the subjects of the curriculum and while there may be differences of opinion regarding the classification of some of the subjects and the number of hours devoted, the purpose of the Syllabus is to be suggestive and helpful and "not designed to interfere with such flexibility in courses of study and freedom in methods of instruction as ought to exist in schools of pharmacy."

The discussions, suggestions and general information found in Section III give information of value for the preparation of state board examinations. Chairman J. G. Beard has ably directed the work of the Committee and the coöperation of the members has resulted in a Syllabus which is not only useful and helpful, but reflects credit on pharmacy. The book is well bound and printed. Size 6″ x 9″, bound in cloth, 168 pages. The sale price for single copies is $2.25, post-paid; for five or more copies $2.00 each post-paid, and may be obtained from Chairman J. G. Beard, Chapel Hill, North Carolina.

Swedish Apotekarkalender for 1932, edited by O. KULLBERG. This publication of 424 pages + is bound in half-leather, printed on paper which shows half-tone prints to advantage. Of outstanding value are the half-tones of Swedish pharmacists, about 1500, accompanied by brief biographical sketches of Swedish pharmacists. The *Kalender* serves a useful purpose not only for Swedish pharmacists but for pharmacists everywhere and the AMERICAN PHARMACEUTICAL ASSOCIATION is indebted to its honorary member, Dr. Knut Magnus Sjoberg, of the Swan Pharmacy, Stockholm, for a copy of this valuable publication and thanks are extended to him. A sketch with accompanying half-tone appears on page 325 and additional data regarding his many activities and honors are given on page 416, among the notices reference is made to his honorary membership in the AMERICAN PHARMACEUTICAL ASSOCIATION.

The Canadian Formulary. Notice was given of the Formulary in the April JOURNAL and reference should have been made to the report by Prof. R. O. Hurst in the February issue, page 160. This answers the purpose of a review. In the "Reference Companion" of about 30 pages, a number of the formulas in this section correspond with those of the N. F. V.

RECENT USAGE OF THE TERM "PYRETHRIN."*

HAROLD H. SHEPARD.[1]

An unfortunate confusion in the use of the term *pyrethrin* exists in the literature of plant chemistry. Buchheim (1) in 1876 proposed the word to designate the active principle in the root of *Anacyclus pyrethrum* (Linn.), or pellitory of medicine. Because *Pyrethrum* was for a long time also the generic name of plants which are the source of insect powder, the term *pyrethrin* and other derivatives of the name *Pyrethrum* have been used recently for the active principles of that insecticide. A brief survey of definitions of *pyrethrum* in recent editions of various medical dictionaries shows that a real confusion, or considerable ambiguity, of terms exists. A few facts concerning the nature and source of pellitory and of insect powder, as well as the history of the term *pyrethrin*, will help in making clear the reason for the existence of such a condition.

Anacyclus pyrethrum (Linn.) De C., belonging to the Compositæ, is commonly known as

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pellitory. It grows principally in northern Africa. The root is used in medicine as a counter-irritant and sialagogue although it is stated in the Dispensatory of the United States of America (2) that this drug is very rarely employed to-day. Pellitory was deleted from the present United States Pharmacopœia X but it was called *pyrethrum* in many of the earlier editions. In Europe, *radix pyrethri, Bertram root* and variations of these names are used. *Anacyclus officinarum* Hayne, the root of which is known by substantially the same names, grows in Germany.

Chrysanthemum species that are the source of insecticidal *pyrethrum* were grown originally in southeastern Europe and southwestern Asia. In this case, it is principally the flower head instead of the root that contains the active compounds. When *pyrethrum flowers* (*flores pyrethri*) are mentioned reference is certainly to the flowers of a *Chrysanthemum* (*pyrethrum*) species. French usage prevents ambiguity with the expression *pyrèthre insecticide*.

Prior to Buchheim's suggestion of the term *pyrethrin* Parisel (3) in 1833 gave a similar name, *pyrétrine*, to an active resin he extracted from pellitory. Thompson (4) has been given credit by Czapek (5) (page 294) for applying the name *pyrethrin* in 1887, although Czapek (page 252) also refers to Buchheim's previous usage (1876). Dunstan and Garnett (6) proposed the name *pellitorine* in 1895 for the physiologically active, crystalline principle of pellitory. They say, "It is very probable that it is the same substance as that isolated, but very imperfectly examined, by Buchheim, in 1876, and named by him pyrethrine." In 1896 Schneegans (7) spoke of *pyrethrin* as the active constituent of *Anacyclus pyrethrum*.

Insect powder was investigated in 1909 by Fujitani (8), who is responsible for the first analytical work of much significance on it. He found a physiologically active ester which he called *pyrethron*. Yamamoto (9) worked with the same substance in 1918 and used Fujitani's name for it. Staudinger and Ruzicka (10) found the principle to consist of two related esters which in 1924 they called *pyrethrins* I and II. They reported that Fujitani's *pyrethron* was the same as their mixture but contained somewhat more than fifty per cent of impurities. Their action in changing an established name is hard to understand. Furthermore, the fact that their name was already in use should have been easily ascertainable from various medical and botanical reference works. In 1927, Ott and Behr (11) pointed out this use of the same name for two widely different chemical products of the respective plants and claimed "pyrethrin" for the principle in Bertram root on the basis of priority. On the other hand, Gulland and Hopton (12) proposed in 1930 to retain Dunstan and Garnett's name *pellitorine* "in preference to the earlier 'pyrethrin' in order to avoid possible confusion with the constituents of *Pyrethri flores*, the dried flowers of pyrethrum species which are used in powdered form as insecticides."

Under the circumstances it might seem obvious that the term *pyrethrin* should be retained for the active principle of pellitory and another name used for that of the insecticide. Fujitani's term *pyrethron* for the latter has priority but it has not been widely accepted and is too similar to be an improvement in nomenclature. On the other hand, pellitory is a drug of minor and waning importance, whereas extracts of pyrethrum flowers are very widely used and are becoming increasingly important as insecticides. The term *pyrethrin* for the active esters in the flowers, though originally incorrectly applied is so generally used by plant chemists, pharmacologists and entomologists that it is neither feasible nor desirable to attempt its restoration to the original usage. However, ambiguity should be avoided by reference to its plant source.

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